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PROPHYLACTIC CHEMOTHERAPY FOR BURNS

DIES ON THE LOCAL AND SYSTEMIC USE OF COMBINED THERAPY

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EVIOUS studies from this unit have shown the local hylactic value in burns of penicillin against *Strepto-* *us pyogenes* (Colebrook et al 1948, Jackson Lowbury, Topley 1951a), of polymyxin against *Pseudomonas* *anea* (Jackson et al 1951b), and, in more limited , of neomycin and of chlorhexidine against *Staphy-* *cus aureus* (Lowbury 1955, 1957) The control of rial colonisation was associated with better clinical ts As resistant variants did not emerge, the agents d were thought suitable for local prophylactic use was more effective in controlling some bacteria than s, however, and it seemed desirable to find an alterna- for penicillin

e therefore made a controlled trial of a cream con- ıg neomycin, chlorhexidine, and polymyxin (N C P) h is active against a wide range of organisms, includ- *tr pyogenes*, *Ps pyocyanea*, and *Staph aureus* Since surgeons do not favour local chemoprophylaxis recommend the use of tulle-gras (e g , Mowlem and son 1954), we used tulle-gras as the control dressing rial in one part of our study

e report here also a small study of the systemic use veral antibiotics in combination for the attempted hylaxis of severely burned patients, and some vations on the use of tetracycline with erythromycin ıe treatment of streptococcal infection of burns

Controlled Trials with N C P Cream

the first trial N C P cream was compared with tulle- and in the second trial N C P cream was compared penicillin cream

P cream contained neomycin sulphate 2 mg , chlor- ine (' Hibitane ') dihydrochloride 1 mg , and polymyxin B per gramme, made up as prescribed for penicillin cream k et al 1943), but with a non-ionic emulsifying wax— ıacrogol 1000 (*B P C*)—in place of ' Lanette wax ' which es the activity of chlorhexidine (Martin 1956) In atory tests we found no evidence that cetomacrogol eres with polymyxin, neomycin, or chlorhexidine, nor these agents interfere with one another

tients included in the trials had fresh burns of full or al skin thickness of less than 15% (in children less than) of the body-surface, which were neither grafted on ssion to the unit nor treated by the exposure method e with even hospital numbers were allocated for treatment N C.P cream, and those with odd numbers for the control aration The cream or control preparation was applied on ission and at every change of dressings, the interval between ications being usually 5 or 6 days From all the burns eriological samples were taken with absorbent cotton-wool swabs (moistened with sterile 10% broth-saline when the burn surface was dry) at all dressings We included in the bacteriological assessment several patients whose burns had the wrong local treatment once only, but these were excluded from the clinical assessment.

Patients in the burns unit were treated with the precautions described by Colebrook (1950) against added infection, including the changing of dressings in a plenum-ventilated room, in more patients than formerly, however, the exposure method was used

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Swabs were inoculated on horse-blood-agar (containing 4% agar to prevent swarming of proteus) and into cooked-meat broth, these were incubated and examined as described by Jackson et al 1951b All strains of *Staph aureus* (i e , coagulase-producing staphylococci) and *Str pyogenes* isolated in the ward were tested for sensitivity to neomycin sulphate and chlorhexidine diacetate by a ditch-plate method, with the Oxford strain of *Staph aureus* included as a sensitive control on each plate, and 50 μg of each antibacterial agent per ml of nutrient agar in the ditch Strains were regarded as sensitive if the zones of inhibition of their growth were similar to those of the control strains By a similar method (but without sensitive control strains) we tested the sensitivity of *Ps pyocyanea*, proteus, and coliform bacilli, from patients in the trial only, to neomycin, chlorhexidine, and polymyxin B, with 50 μg per ml of nutrient agar (4%) in the ditch Most of these strains were also tested for sensitivity to an N C P mixture at the same concentration

Because neutralisers for the N C P combination were not available, we tested for the possible transfer on swabs of inhibitory levels of these agents to the solid and fluid culture media (e g , Jackson et al 1951b)

Bacteriological Results

Table I records the colonisation of burns by pathogenic bacteria between the day after admission and the end of the 3rd week in the first trial of N C P cream (comparison with tulle-gras) The pathogens considered were *Str pyogenes*, *Staph aureus*, *Ps pyocyanea*, members of the proteus group, and unclassified coliform bacilli (including *Escherichia coli*, *Klebsiella aerogenes*, and other species) No distinction is made in this table between burns from which an organism was isolated repeatedly and those from which it was isolated once only There is a striking difference in respect of colonisation by *Staph aureus* and *Str pyogenes* Every group of organisms appeared more often in the burns treated with tulle-gras whether the burns or the patients were compared, but the differences were smaller with gram-negative bacilli than with pyogenic cocci

TABLE I—BACTERIA IN BURNS DURING FIRST PROPHYLACTIC TRIAL N C P CREAM COMPARED WITH TULLE-GRAS

Bacteria	Local treatment	Bacteria isolated from burns (days 1–21)						
		+	±	−	Total	+ or ± (%)	$\chi^2_{[1]}$	P
Str pyogenes	N C.P cream	4	1	70	75	*6 7*	7·55	<0·01
	Tulle-gras	22	0	71	93	*23 7*		
Staph aureus	N C.P cream	15	6	54	75	*28 0*	55 9	<0·001
	Tulle-gras	82	0	11	93	*88 2*		
Ps pyocyanea	N C.P cream	9	8	58	75	*22 7*	0 8	>0·05
	Tulle-gras	16	12	65	93	*30 1*		
Proteus	N C.P cream	9	2	64	75	*14 7*	0 6	>0 05
	Tulle-gras	17	2	74	93	*20·4*		
Coliform bacilli	N C.P cream	10	4	61	75	*18 7*	3 8	0 05
	Tulle-gras	25	6	62	93	*33 3*		

Table II shows the frequency of absent or very scanty bacterial growth from burns Those treated with tulle-gras showed progressively fewer swabs without growth or with scanty growth, and all swabs taken after the 14th day yielded bacteria, of those taken after the 14th day from burns treated with N C P cream, however, 45% showed no growth, and 61% showed no growth on direct inoculation of solid medium.

The good prophylactic action against *Ps pyocyanea* observed

TABLE II—BURNS WITHOUT BACTERIAL GROWTH OR WITH SCANTY GROWTH DURING THE FIRST TRIAL OF N C P CREAM

Day of burns sample	No of swabs from burns treated with local application									
	N C P cream					Tulle-gras				
	N G*	± †	Total	N G (%)	N G & ± (%)	N G	±	Total	N G (%)	N G & ± (%)
1–3	12	14	36	*33*	*72*	*5*	2	42	*12 0*	*17 0*
4–7	22	18	58	*38*	*69*	2	3	71	*2 8*	*7·0*
8–14	21	11	60	*35*	*53*	1	3	93	*1 1*	*4 3*
15–21	23	8	51	*45*	*61*	*0*	1	58	*0 0*	*1 7*

* N G = no bacterial growth. † ± = scanty growth (only in fluid culture)

in an earlier trial of polymyxin cream (Jackson et al 1951b) was not reproduced in this comparison of N C P cream with tulle-gras In the earlier study, however, penicillin cream was used as the control, and because the burns were kept moist in this way their surface was probably more favourable for the growth of gram-negative bacilli than the drier surface under tulle-gras We therefore undertook the second trial of N C P cream, in which penicillin cream (1000 units per g) was the control material The results of this trial (table III) show that the burns dressed with N C P cream had a significantly lower rate of infection with *Ps pyocyanea* (4/48, 8 3%) than those dressed with penicillin cream (28/78, 36%) Again the incidence of *Staph aureus* was significantly lower in the burns dressed with N C P cream, but the difference was smaller when the control material was penicillin cream rather than tulle-gras Proteus and coliform bacilli were not significantly less common with N C P cream than with penicillin cream *Str pyogenes* appeared less often in the burns treated with N C P than in those treated with penicillin cream, which acquired streptococci more often than in former trials (e g, Jackson et al 1951b)

Prophylaxis in Burns of Different Extent

We made separate analyses of the incidence of *Staph aureus* during the first 3 weeks of the first trial in burns of less than 5% and in burns of 5% or more of the body-area (table IV) The N C P cream had a prophylactic action against *Staph aureus* in the larger as well as the smaller burns, though the effect was not as great in the larger ones

Prophylaxis in Burns of Full Skin Thickness

A separate analysis of bacteriology in burns of full skin thickness, which usually required skin-grafting, is shown in table V In full-skin-thickness burns of the first trial the prophylactic action of N C P cream was better than that of the control treatment, but in the second trial staphylococci were infrequent in either group, and colonisation by the other pathogens differed little

Sensitivity of Bacteria from Burns to N C P Cream

Table VI shows the results of sensitivity tests during 3-month periods before the first trial of N C P cream, in the early part of the first trial, and at the end of the second trial All the strains of *Staph aureus, Str pyogenes,* and *Ps pyocyanea* were sensitive to the N C P mixture Proteus and coliform bacilli, which are not included in the table, were usually sensitive to the mixture, proteus was always resistant to polymyxin, but usually sensitive to chlorhexidine and neomycin, coliform bacilli, especially citrate-utilising (Koser-positive) strains, were sometimes resistant to the N C P mixture Since the concentration of antibacterial agents applied to the burns was much greater than 50 µg per ml, "resistance" as defined above was sometimes theoretically compatible with prophylactic value

TABLE III—BACTERIA IN BURNS DURING SECOND PROPHYLACTIC TRIAL N C P CREAM COMPARED WITH PENICILLIN CREAM

Bacteria	Local treatment	Bacteria isolated from burns (days 1–21)						
		+	±	−	Total	+ or ± (%)	$\chi^2_{[1]}$	P
Str pyogenes	N C P cream	1	0	47	48	*2 1*		
	Penicillin cream	7	0	71	78	*8 9*		
Staph aureus	N C P cream	9	4	35	48	*27 1*	7 5	<0·01
	Penicillin cream	39	3	36	78	*53 8*		
Ps pyocyanea	N C P cream	3	1	44	48	*8 3*	10 5	<0 01
	Penicillin cream	22	6	50	78	*35 9*		
Proteus	N C P cream	2	2	44	48	*8 3*	0 8	>0·05
	Penicillin cream	5	7	66	78	*15·4*		
Coliform bacilli	N C P cream	10	4	34	48	*29 2*		
	Penicillin cream	15	8	55	78	*29 5*		

CLINICAL RESULTS OF FIRST TRIAL

In this trial N C P cream was compared with tulle-gras

The "Take" of Split-skin Grafts

The results of the first skin-grafting operations are summarised in table VII Whether *Str pyogenes* was present or not, graft failure (less than 80% take) was significantly commoner in patients whose burns were dressed with tulle-gras than in those dressed with N C P cream

Healing-time

This was defined as the number of days from the time of injury until the burn was completely healed, with no small crusts remaining But there are serious difficulties in interpreting this criterion, because even minute areas of whole-skin loss (e g, less than $^1/_4$ in in diameter) may remain unhealed for many days, and a burn which is almost completely healed in 25 days may, by this definition, take twice as long to heal completely In burns of full-skin thickness, healing-time was a less satisfactory measure than grafting results, for few burns were examined daily, and the last crust might have separated at any time after the previous dressing In burns of partial skin thickness, which range from superficial blistering to destruction of almost the whole thickness of the skin, healing-times vary widely and are virtually useless for assessing prophylactic measures on a small series In the first trial the mean healing-time (table VIII) of burns of full skin thickness treated with N C P cream was 7 5 days shorter than that of burns treated with tulle-gras This difference was probably largely attributable to the more frequent delay in healing after failure of skin-grafts in burns dressed with tulle-gras The healing-time of burns from the day of operation was, on average, about 11 days longer (37 5±7 1) with tulle-gras than with N C P cream (26 4±3 6 days)

TABLE IV—PROPHYLACTIC VALUE OF N C P CREAM IN BURNS OF DIFFERENT AREA

Local treatment	—	*Staph aureus* isolated from burns of	
		<5% body area	*5% or more body-area*
Tulle-gras	Patients	11/11	28/28
	Burns	18/19	64/74
N C P cream	Patients	3/7	11/21
	Burns	4/18	*17/57*

TABLE V—PROPHYLACTIC VALUE OF N C P CREAM IN BURNS OF FULL SKIN THICKNESS

Local treatment	Trial	Burns colonised by		
		Staph aureus	*Str pyogenes*	*Ps pyocyanea*
N C P cream	1	8/20	1/20	3/20
	2	3/12	0/12	2/12
Tulle-gras	1	27/27	8/27	9/27
Penicillin cream	2	3/12	2/12	4/12

Clinical Infection

Cellulitis, lymphangitis, and septicæmia were not found in either group Local pain, swelling, and lymphadenitis appeared in three patients dressed with N.C.P. cream, and in four dressed with tulle-gras.

Other Clinical Features

The average time before the sloughs of full-skin thickness burns loosened, making the area ready for grafting, was 20·1 days in patients dressed with tulle-gras, and 21·6 days in those dressed with N.C.P. cream; we had expected that the drier surface under tulle-gras would cause a slower separation of slough. Dressings were adherent and painful to remove in two burns treated with N.C.P. cream, and in six treated with tulle-gras.

Systemic antibiotics were required for the treatment of clinical infection in fewer burns treated with N.C.P. cream than with tulle-gras.

The mean morning (6 A.M.) and evening (6 P.M.) temperature, and the mean of the highest temperature each week of patients in the trial was calculated for evidence that the generalised effects of infection could be controlled by prophylactic treatment. The results showed insignificant differences between the two groups of patients.

CLINICAL RESULTS OF SECOND TRIAL

In this trial N.C.P. cream was compared with penicillin cream, and the proportion of full-skin-thickness burns was smaller.

The prophylactic value of N.C.P. cream, shown in the bacteriological analysis of the whole series, was not apparent in the separate analysis of bacteria in full-skin-thickness burns (table V). It was not surprising, therefore, that no significant difference was found in skin-grafting results and healing-times of full-skin-thickness burns included in the clinical assessment. None of the twelve burns treated with N.C.P. cream and only one of the eleven treated with penicillin cream, and requiring operation, showed failure of skin-grafts. If the criterion of success in grafting was 100% take, the results favoured N.C.P. cream; of twelve burns so treated eight were successfully grafted, as compared with two successes in eleven grafting operations on burns dressed with penicillin cream. Systemic chemotherapy was required more often for the treatment of infection in burns treated with penicillin cream than in those treated with N.C.P. cream.

TABLE VI—SENSITIVITY OF BURN FLORA (BY DITCH-PLATE TESTS) TO NEOMYCIN, CHLORHEXIDINE, AND POLYMYXIN

Bacteria	Period	% strains sensitive to				Total strains*
		N.C.P. mixture	Neomycin	Chlorhexidine	Polymyxin	
Str pyogenes	Before trial	100	0	100		113
	First ,,	100	8	100		281
	Second ,,	100				196
Staph aureus	Before trial	100	100	100		1435
	First ,,	100	100	100		1688
	Second ,,	100				2804
Ps pyocyanea	Before trial	100	4	82	100	72
	First ,,	100	0	100	100	211
	Second ,,	100	0	74	100	23

* All strains of *Str pyogenes* and *Staph aureus* isolated in the wards, and all strains of *Ps pyocyanea* isolated from patients in the trial during these periods.

Sensitisation.—No skin eruptions or other evidence of sensitisation to the prophylactic agents were detected in either trial.

Comparability of cases in the trials.—The patients in the treatment and control groups of the first trial of N.C.P. cream were comparable in respect of age, sex, and area of burns; in the smaller second trial the average age of patients in the two groups differed by 10 years, but this is unlikely to have influenced the clinical results.

Trial of Systemic Chemoprophylaxis

Patients with extensive burns run a considerable risk of dying from the severe pyrexial or septicæmic illness which is associated with heavy colonisation by *Staph aureus*, *Ps pyocyanea*, and various bacteria of the proteus and coliform groups (Liedberg et al. 1954, Jackson et al. 1960). Our practice has been to protect severely burned patients with intramuscular penicillin (1 million units daily) against the risks of invasion by *Str pyogenes*, but this organism appears irregularly, is easily eliminated by chemotherapy, and has not of recent years been associated with invasive infection in burned patients. For prophylaxis against the bacteria which are more apt to cause fatal infection other antibiotics, preferably in combination, are more likely to have clinical value.

TABLE VII—RESULTS OF SKIN-GRAFTING IN FIRST TRIAL OF N.C.P. CREAM

Patients	Local treatment	Successful grafts (80% or more "take")	Graft failures (<80% "take")	Graft successes (%)	Significance tests
All in trial	N.C.P. cream	18	2	*90*	$\chi^2 = 10·3$
	Tulle-gras	14	20	*41*	$P < 0·01$
Excluding those with *Str pyogenes* in burns	N.C.P. cream	16	2	*89*	$\chi^2 = 8·06$
	Tulle-gras	12	16	*43*	$P < 0·01$

TABLE VIII—HEALING-TIME AND OTHER DETAILS OF PATIENTS IN TRIALS OF N.C.P. CREAM

—	First trial		Second trial	
	N.C.P. cream	Tulle-gras	N.C.P. cream	Penicillin cream
No. of patients in clinical assessment	25	35	13	15
Mean healing-time (days) of patients with full-skin-thickness burns				
From day of injury	51·6	59·1	41·5	41·5
From day of operation	26·4	37·5		
% patients requiring systemic chemotherapy	*33*	*46*	*30*	*73*

A controlled trial was therefore made in which the prophylactic effects of combined systemic therapy with four antibiotics were compared with those in patients having systemic penicillin.

Patients with burns, whose estimated case-mortality was more than 10% (Bull and Fisher 1954) were allocated alternately to two groups. Antibiotic prophylaxis in each group was started soon after admission to the unit, and was continued until the first operation, or until 7 days after the injury if the burns were excised and grafted on admission.

Patients in the first group were treated with penicillin intramuscularly (500,000 units 6-hourly in adults, or half that dose in children under 5); from the 3rd day, phenoxymethyl penicillin was given by mouth (250 mg. 6-hourly to adults, and half to children under 5). The patients in the second group were treated with chloramphenicol, tetracycline, erythromycin, and polymyxin B—a combination of antibiotics which would, in our experience, cover a wider range of burn pathogens than any other available at the time. While intravenous infusions were running, tetracycline and erythromycin were given intravenously, and chloramphenicol and polymyxin were given intramuscularly; from the 3rd day all antibiotics except polymyxin were given by mouth unless the patient was vomiting, in which case the intramuscular route was used. The doses given to adults were: tetracycline, 250 mg. 6-hourly intravenously or by mouth; erythromycin, 300 mg. 6-hourly by mouth and 250 mg. intramuscularly or intravenously; chloramphenicol, 500 mg. 6-hourly intramuscularly or by mouth; polymyxin B, 50 mg. 6-hourly intramuscularly. Penicillin cream was applied locally to all burns which were not excised and grafted on admission. Patients in the first group whose clinical condition necessitated the use of antibiotics other than penicillin, and patients in the second group who showed evidence of toxic reaction to the antibiotics, did

TABLE IX—BACTERIA IN BURNS DURING TRIAL OF SYSTEMIC CHEMOPROPHYLAXIS FOR SEVERELY BURNED PATIENTS

Bacteria	Systemic treatment	Bacteria isolated from burns (days 1–21)				
		+	±	–	Total	+ or ± (%)
Str pyogenes	Combined therapy *	0	0	101	101	0·0
	Penicillin	0	0	94	94	0·0
Staph aureus	Combined therapy	65	4	32	101	68·3
	Penicillin	42	0	52	94	44·7
Ps pyocyanea	Combined therapy	24	21	56	101	44·6
	Penicillin	10	14	70	94	25·5
Proteus	Combined therapy	23	5	73	101	27·7
	Penicillin	17	1	76	94	19·1
Coliform bacilli	Combined therapy	55	7	39	101	61·4
	Penicillin	59	9	26	94	72·3

* Systemic treatment with chloramphenicol, erythromycin, tetracycline, and polymyxin B.

not complete the course and were excluded from bacteriological assessment from that time.

Bacteriological studies were the same as those made on organisms from patients in the trials of local prophylaxis, with sensitivity tests to the relevant antibiotic by the ditch-plate method on all strains of *Staph aureus*, *Str pyogenes*, and gram-negative bacilli. When possible blood-cultures were taken on days 1, 7, 14, and 21, and whenever the temperature rose to 103°F or higher. In addition to cooked-meat-broth cultures, which were examined for aerobic and anaerobic organisms, blood-agar plates were inoculated directly with 2 or 3 drops of the patient's blood.

Twelve patients were included in the penicillin series and eleven in the combined-chemotherapy series; in view of the results in these patients we did not continue the trial.

BACTERIOLOGICAL RESULTS

The bacteriology of the burns during the first 3 weeks (or while they were in the trial) is shown in table IX. *Str pyogenes* did not appear in any burn, but the other organisms were abundant and no less common in patients treated with combined antibiotics than in those treated with penicillin. *Staph aureus*, *Ps pyocyanea*, and proteus were commoner in the former, coliform bacilli were commoner in the latter.

While there was no evidence that combined therapy had any prophylactic effect on the flora of the burns, it may conceivably have helped to prevent septicæmia in some patients. In the patients treated with penicillin, 21 of the 42 cultures taken (50%) were positive; those treated with combined chemotherapy yielded 11/33 (33·3%) positive cultures. But the difference is not statistically significant. Bacteria isolated from blood-cultures included *Staph aureus*, *Ps pyocyanea*, proteus, coliform bacilli, and *Str fæcalis*. *Str pyogenes* did not grow in any blood-culture. Mixed cultures were sometimes found, and different organisms were sometimes isolated from successive positive blood-cultures.

Table X shows the proportions of staphylococci, from patients in the trial, which were resistant to the antibiotics. Resistance to penicillin was very common in both groups throughout the trial, but the proportion of strains resistant to the other antibiotics (in particular to chloramphenicol) increased, and this was generally more pronounced in material from patients having combined therapy. After the 4th month, during which no patients were in the trial, the frequency of chloramphenicol resistance fell, but it rose again in both groups when patients were again admitted to the trial, and reached higher levels in the patients having combined therapy than in those having penicillin.

TABLE XI—CLINICAL FINDINGS IN TRIAL OF SYSTEMIC CHEMOPROPHYLAXIS

Details of patients	Patients treated with	
	Systemic penicillin	Systemic comb chemotherap (tetracycline, polymyxin, chloramphenic and erythromy
No.	12	11
Females	8	7
Average age (yr.)	21·7	20·4
Average total area of body burned (%)	43·5	38·5
Average total area of full-thickness skin loss (%)	38	30
No. of deaths	9	6
Clinical septicæmia	6	3
Respiratory complications	7	3 (2 after antibiot had been stopp
Mean pulse-rate		
1st week	123	116
2nd ,,	128	125
3rd ,,	116	114
Mean respiration-rate		
1st week	30	27
2nd ,,	31	30
3rd ,,	27	29

CLINICAL RESULTS

The treatment schedule could not be maintained in all cases. Diarrhœa, vomiting, and "needle-shyness" made it necessary to stop one or more of the antibiotics, or to change the way they were administered. If the area of full skin thickness was reduced by skin-grafting or spontaneous healing to less than 10% of the body-surface, and the patient appeared to be well, antibiotic prophylaxis was stopped. If other antibiotics (e.g., novobiocin or vancomycin) were considered necessary, they were given.

Table XI summarises the main details. The patients in the two groups were comparable in respect of age, sex, and severity of burns. In most respects other than antibiotic prophylaxis, their treatment was identical—e.g., in both groups a variety of infusion fluids was used (plasma, plasma and albumin, albumin, plasma, albumin, and blood, albumin and blood) and one patient in the combined-chemotherapy series had serum infusions. The chief disparity in treatment was that in the penicillin series five patients' burns were excised on the 1st day, whereas in the combined chemotherapy series there was only one such case, but this difference is unlikely to have affected the results of the trial (see Jackson et al. 1960).

Mortality

The mortality in both groups was higher than that expected in patients of the same age and estimated area of burn, as shown in the mortality chart of Bull and Fisher (1954). But the

TABLE X—RESISTANCE OF *Staph aureus* FROM BURNS OF PATIENTS IN TRIAL OF COMBINED SYSTEMIC PROPHYLAXIS

Month of trial	Patients on combined prophylaxis					Patients on penicillin prophylaxis				
	% strains resistant to				Total strains	% strains resistant to				Total strains
	Chloramphenicol	Erythromycin	Tetracycline	Penicillin		Chloramphenicol	Erythromycin	Tetracycline	Penicillin	
1	0	20	20	100	5	0	30	50	90	10
2	6	33	96	96	30	0	100	97	100	37
3	40	67	92	100	104	21	79	75	96	24
4					0					0
5	0	100	58	100	12	0	80	77	93	30
6	53	93	93	96	76	2	89	51	100	41
7	71	93	93	99	105	16	60	60	100	74
8	43	84	87	100	37	0	50	50	60	10
9	12	100	100	100	49	0	25	25	25	4

outcome was slightly worse in the patients having penicillin. In the age-group 21–40 years, observed deaths were less than expected with combined chemotherapy, but greater than expected with penicillin.

Respiratory Complications

Bronchitis, bronchopneumonia, atelectasis, and other respiratory complications, detected either clinically or at necropsy, were more frequent with penicillin (7/11) than with combined chemotherapy (3/12). This is consistent with the patients' significantly higher mean respiratory rates in the first 2 weeks in the penicillin series (30·0±0·7 and 31·1±0·8) than in the combined chemotherapy series (26·8±0·6 and 29·5±0·8) (S.E. of difference of mean 0·86 and 1·15). Most of the deaths (10/15) were during these first 2 weeks. The mean pulse-rate of the patients treated with penicillin was higher, but the mean temperature was almost the same in the two series.

Urinary Infections

During the "shock" phase all the patients had indwelling catheters for at least 48 hours. Only one of the eleven patients treated with combined chemotherapy and two of the twelve treated with penicillin showed bacterial growth in urine-culture. One patient in the penicillin group was found at necropsy to have bilateral pyelonephritis, although the primary cause of death was inhalation of vomit.

TABLE XII—INFECTION OF BURNS WITH *Str. pyogenes* IN TWO WARDS, 1955–59

Year	Treatment for *Str. pyogenes* in burns	Tetracycline-resistant *Str. pyogenes* (%)	Patients with *Str. pyogenes* in burns (mean % per month)	Mean no. of patients in burns unit per month
1955	Tetracycline by mouth	*28·6*	*10·2*	68·3
1956	Tetracycline by mouth, later erythromycin by mouth	*55·8*	*13·0*	74·8
1957	Erythromycin by mouth	*37·4*	*16·7*	60·8
1958	Combined tetracycline and erythromycin by mouth	*0·0*	*10·7*	63·3
1959	Combined tetracycline and erythromycin by mouth	*0·0*	*8·1*	68·2

Leucopenia

Total and differential leucocyte-counts were made weekly. Only one patient having combined chemotherapy had a total count of less than 8000 per c.mm. (4600), and this returned to normal after chemotherapy was stopped. Two patients in the penicillin series had leucopenia (one with a count of 3800 per c.mm.).

Septicæmia

Patients were said to have septicæmia when they were severely ill, with a high temperature (usually over 102°F) and a positive blood-culture. Septicæmia was diagnosed in six patients in the penicillin series and in three in the combined-chemotherapy series.

Other Complications

Three patients treated with combined antibiotics, and one treated with penicillin had diarrhœa, one in each group had a mild monilia infection. One of the penicillin series had a transient urticaria. Renal failure occurred in three patients having combined chemotherapy, but in two it had arisen before chemotherapy was started, and the third patient was found at necropsy to have nephrosclerosis.

Combined Chemotherapy for Streptococcal Infections

The failure of penicillin to eliminate *Str. pyogenes* from burns—presumably through interference by penicillinase-producing organisms—prompted us to make trials of tetracycline and erythromycin given by mouth, each of which was strikingly effective (Lowbury and Cason 1954).

Unfortunately tetracycline-resistant *Str. pyogenes* appeared and became increasingly common until, in 1956, over 50% of the streptococci isolated were resistant to tetracycline, and *Str. pyogenes* often persisted after treatment with tetracycline. We therefore changed to erythromycin for the routine treatment of streptococcal infection of burns. After this, tetracycline-resistant streptococci gradually became less common, but erythromycin-resistant streptococci began to appear at the end of 1957 (Lowbury 1958).

Since then we have combined erythromycin and tetracycline in full dosage for all burns infected with *Str. pyogenes*. The results have been rewarding, for no strain of *Str. pyogenes* resistant to tetracycline or to erythromycin has been isolated during 1958 and 1959, the streptococci have nearly always disappeared from the burns after 3 or 4 days' treatment.

This improvement has been associated with some reduction in the incidence of streptococcal infection of patients in the unit (table XII). These figures are not dramatic, and they do in fact somewhat exaggerate the benefits conferred by successful therapy, for the year 1957, with the most streptococcal infection, was also the year when the trial of tulle-gras led to an increase in the incidence of streptococcal infection. A small proportion of patients with burns infected by *Str. pyogenes* carried the organism either on their burns or in the upper respiratory tract on admission to the unit, the largest number of patients with streptococci (nineteen) were admitted during 1955, a year when the infection-rate with *Str. pyogenes* was relatively low.

Discussion

Prophylaxis with antibiotics in surgery has been widely condemned, except when the risks of infection are high. This is reasonable, for the routine prophylactic use in hospital of such agents as tetracycline, chloramphenicol, and erythromycin must increase the number of resistant staphylococci and other organisms in the environment. Similar arguments are sometimes raised against the local application of antibiotics to burns, but the experience described in this paper shows that the most obviously important pathogens in burns do not appear to produce resistant variants to three effective agents (neomycin, chlorhexidine, and polymyxin) applied locally. After similar treatment with tetracycline and chloramphenicol in earlier trials, resistant staphylococci appeared quickly.

The exposure method of treatment, and the use of tulle-gras dressings, have been recommended for burns because they allow the surface to dry, and a dry burn is believed to discourage bacterial growth. Moist dressings (e.g., a cream) without antibiotics will undoubtedly aid bacterial growth, but if the cream contains antibiotics, the disadvantage of moisture may be offset. The relative merits of antibiotics and dryness were tested in our first trial. This showed that *Staph. aureus* and *Str. pyogenes* were much less common in burns treated with N.C.P. cream than in a comparable series of burns dressed with tulle-gras, in burns of full skin thickness, the results of split-skin grafting were significantly better in the patients treated with N.C.P. cream, the mean healing-time from operation being 11 days shorter than in patients treated with tulle-gras. Similar clinical results were obtained in our earlier trials with single antibiotics in the control of infection with *Str. pyogenes* and *Ps. pyocyanea* (Jackson et al. 1951a and b, Lowbury and Cason 1954), indeed, a greater effect on healing-time was observed in a trial of polymyxin for more extensive burns. If, in the trial reported here, burns which became infected with *Str. pyogenes* were left out of the analysis, the results of skin-grafting were still found to be much better in the series treated with N C P cream, perhaps because of the exclusion of *Staph aureus*

Unlike the gram-positive cocci, *Ps pyocyanea* was not significantly commoner in the burns treated with tulle-gras than in those treated with N C P cream This contrasts with our finding in an earlier trial when polymyxin cream was compared with penicillin cream (Jackson et al 1951a) But in the second trial of N C P cream reported above the control series of burns was treated with penicillin cream and showed significantly more *Ps pyocyanea* (as well as more *Staph aureus*) than the series dressed with N C P cream These findings suggest that *Ps pyocyanea* may be suppressed in burns either by using polymyxin cream, or by keeping the surface dry This is consistent with the knowledge that *Ps pyocyanea* and other gram-negative bacilli are more sensitive than the gram-positive cocci to the lethal effects of drying We are now trying to find whether antibiotics directed against the gram-positive cocci can be successfully combined with dry conditions directed against the gram-negative bacilli

The shorter healing-time of burns protected with N C P cream was probably due largely to the better results of skin-grafting in these burns Bacterial growth (even of *Str. pyogenes*) does not obviously interfere with the healing of partial-skin-thickness burns—except, perhaps, those which are deep and might be converted to full-thickness lesions by bacteria Application of antibacterial preparations to superficial burns probably confers no great advantage unless they are treated in hospital, when the suppression of bacterial contaminants is part of the prevention of cross-infection

Our attempt to protect severely burned patients against infection by systemic treatment with a combination of chloramphenicol, tetracycline, erythromycin, and polymyxin was less successful, and, in contrast with the studies of local prophylaxis, it illustrates the futility of attempting prophylaxis with agents against which the burn flora can readily acquire resistance Patients treated with this antibiotic combination actually showed more frequent colonisation by *Staph aureus* and some gram-negative bacilli (including *Ps pyocyanea*, which was always sensitive to polymyxin) than did those having penicillin The numbers of chloramphenicol-resistant staphylococci from patients treated with the antibiotic mixture increased strikingly, and other patients in the ward showed a smaller increase of resistant strains presumably acquired by cross-infection Despite these unsatisfactory bacteriological results, it seemed that prophylaxis with combined antibiotics may have had some clinical effect, for fewer cases of septicæmia and fewer respiratory complications arose among the patients having this treatment than among those treated with systemic penicillin

Successful therapy of established infections reduces the reservoir of pathogens and should reduce cross-infection In burns, chemotherapy can be relied upon to remove the infecting organisms only if these are streptococci of group A, in our crowded burns unit even the combination of tetracycline and erythromycin by mouth for every streptococcal infection did not greatly reduce the frequency of streptococcal cross-infection, though it eradicated strains of *Str pyogenes* resistant to these antibiotics and as a result enhanced the therapeutic effect

The difficulties of protecting extensive burns, especially during management of the "shock" phase, are very great and may be insuperable even with the most elaborate measures at present available, but a careful attempt is needed to assess the value of strict isolation and of improved methods of physical cover or enclosure Although such protection is specially important in the more extensive burns, every burned patient in hospital is a potential source of cross-infection and should be treated with the isolation measures used for cases of infective disease

Summary

The local application of a prophylactic cream to burns of less than 15% (in children less than 10%) of the body-area was studied in two controlled trials The cream (N C P) contained neomycin 2 mg , chlorhexidine dihydrochloride 1 mg , and polymyxin B 1 mg per gramme, made up with cetomacrogol (*B P C*) emulsifying wax In the first trial the control patients' burns were dressed with tulle-gras, and in the second trial with penicillin cream (1000 units per g)

Between a third and a half of the burns dressed with N C P cream in the first trial remained free from bacteria for 3 weeks During that time *Staph aureus* appeared on agar-cultures from 82/93 (88%) of the burns dressed with tulle-gras, but from only 15/75 (20%) of those dressed with N C P cream, by similar tests *Str pyogenes* appeared in 22/93 (24%) of burns dressed with tulle-gras, and in 4/75 (5%) dressed with N C P cream The prophylactic advantages of N C P cream against the gram-negative bacilli were less *Str pyogenes*, *Staph aureus*, and *Ps pyocyanea* from burns were always sensitive to N C P cream Clinical assessment in burns of full skin thickness also favoured N C P cream—e g , 20/34 (59%) of skin-grafting operations failed (showing less than 80% take) when the burns had been dressed with tulle-gras, but only 2/20 (10%) failed when they were dressed with N C P cream The mean healing-time from the day of operation of burns treated with tulle-gras was 11 days longer than that of burns treated with N C P cream

In the second trial, *Staph aureus*, *Ps pyocyanea*, and even *Str pyogenes* were commoner in burns treated with penicillin cream than in those treated with N C P cream

Evidence from the two trials suggested that added infection with *Ps pyocyanea* can be partially controlled by a cream containing polymyxin, or (to a lesser extent) by keeping dry the surface under dressings—e g , by using tulle-gras

In a small controlled trial on extensively burned patients, prophylaxis by systemic penicillin was compared with that of a combination of systemic chloramphenicol, tetracycline, erythromycin, and polymyxin *Str pyogenes* was not isolated from either group Colonisation by other bacteria was not less frequent in the burns of patients who had combined antibiotic prophylaxis than in those given penicillin Among the patients who had penicillin were more cases of septicæmia and more respiratory complications The numbers of staphylococci resistant to chloramphenicol increased considerably during the trial

Since the introduction of treatment for *Str pyogenes* infection of burns with a combination of erythromycin and tetracycline, no streptococci resistant to either of these antibiotics have been isolated from burns in the unit, but the frequency of streptococcal cross-infection of burns has only been slightly reduced

We are grateful to our colleagues, Mr D M Jackson and Dr J P Bull, for valuable advice, to Sister M Nichols and Sister E Rubini for cooperation in the trials, and to Mr L Hurst and Mrs J Pagett for technical assistance We also wish to thank the Wellcome Research Laboratories and Pfizer, Ltd , for supplies of polymyxin B, I C I (Pharmaceuticals) for chlorhexidine, and Upjohn of England, Ltd , for neomycin sulphate

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HÆMATEMESIS AND *MELÆNA*

THEIR EARLY RADIOLOGICAL INVESTIGATION

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Early surgical control of massive bleeding from the stomach or duodenum was recommended by Finsterer (1939) as long ago as 1918, but only with the improved anæsthetic and surgical techniques of recent years has such a policy been widely adopted Avery Jones (1947, 1952) has shown that emergency gastrectomy is particularly indicated in patients over 50 with good clinical evidence of chronic peptic ulcer who bleed again after admission to hospital The greatest reduction of mortality in hæmatemesis can be achieved only if an early decision for or against operation is made in suitable cases

Decisions as to correct treatment of the patient with hæmatemesis most often depend on clinical judgment, but the radiologist can play an important part in assisting his clinical colleagues in the selection of patients for urgent surgical intervention This paper describes a simple bedside radiological investigation which can be of diagnostic value in the acute stages of bleeding

Previous Methods of Radiological Investigation in Hæmatemesis

Clearly the radiological techniques used to elucidate the cause of bleeding in hæmatemesis should not aggravate bleeding or produce shock, and this difficulty has complicated the radiologist's task for many years

Hampton (1937) devised a modification of the standard barium-meal technique which he considered safe in the presence of bleeding The investigation was performed in the X-ray department with the patient supine Thick barium suspension was drunk and then slight side-to-side rotation was employed to outline the whole of the stomach and duodenum The gastric air-bubble was used to produce a double contrast effect Hampton emphasised the importance of examining the posterior and superior walls of the duodenum, where most bleeding ulcers are situated Palpation and the use of the compression cone were considered dangerous because of the likelihood of provoking hæmorrhage, but screen examination was believed to be essential This method, known as the Hampton technique, has been the standard procedure used by radiologists

Bohrer (1941) agreed that the elimination of manipulation was essential if further hæmorrhage was to be avoided Schatzki (1946) criticised the moving of the patient from the ward to the X-ray department, and Heuer (1946) felt that the method was not without risk The tendency has been to delay radiological investigation until at least two weeks after bleeding has stopped, or until the physician thought that additional hæmorrhage would not be provoked (Eads 1946) The limitations of Hampton's method have undoubtedly restricted its application Thus Elmer et al (1950), who examined 58 patients by this technique within three days of admission, found a significant lesion in 44, but they excluded patients with evidence of shock and those to whom intravenous fluids were being administered These include patients in whom the clinician is most anxious to establish the cause of bleeding

A *modification of the Hampton technique, using palpation* and a pressure cone, was described by Ritvo et al (1951), and its clinical application was reported by Zamchek et al (1952a and b) It was claimed that emergency radiological investigation could be safely undertaken in most patients after hæmatemesis The examination was postponed in the presence of continued bleeding or shock, and required a fasting period of eight to twelve hours 74 of 123 patients were examined within forty-eight hours of admission to hospital, and a further 19 within the next twenty-four hours The radiological diagnosis achieved by early investigation was later confirmed in 92 patients, but the results were conflicting in 14 12 patients bled severely after their return to the ward

Knowles et al (1952) investigated 80 of 100 patients admitted to hospital with upper gastrointestinal bleeding, but those in shock were excluded Hampton's technique was used, with the addition of oblique views of the œsophagus, and prone oblique views of the stomach and duodenum About thirty minutes was needed for each investigation, and a second barium-meal examination was considered essential when the patient was ambulant Accurate diagnosis was achieved in 80%, but these figures exclude patients in whom no diagnosis was made Schatzki and Blade (1958) examined 108 patients by Hampton's method, 76 in the first thirty-six hours after admission, and found a cause for bleeding in 76%

Because of the considerable diversity of opinion as to the safety of early radiological investigation of patients bleeding from an unknown lesion in the gastrointestinal tract, the method has never been widely accepted Modifications aimed at increasing its diagnostic accuracy, by the introduction of manipulation and the use of pressure cones, have not improved the results but have almost certainly added to the danger Dissatisfaction with such methods led Cantwell and Johnstone (1959) to devise a procedure which could be applied to patients in the acute stages of hæmatemesis without moving them from bed A similar technique has been adopted at the Central Middlesex Hospital by the departments of gastroenterology and radiology

Method of Ward Radiological Investigation

At the Central Middlesex Hospital early radiological examination of patients admitted with hæmatemesis and/or melæna has been part of a combined investigation which also includes estimation of nocturnal gastric acidity and gastroscopy (Chandler, Cameron, Street, and Nunn 1960) Radiological examination is undertaken in the ward on the day after admission, using whenever possible the same team of senior radiographer, student radiographer, and porter

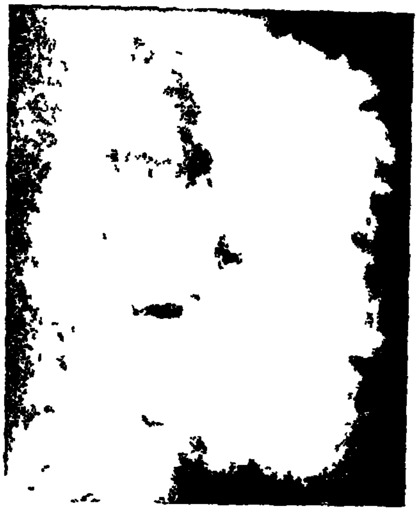

Fig 1—Ward barium-meal examination of a man, aged 54, admitted after hæmatemesis

Note moderate sized benign gastric ulcer This patient underwent emergency partial gastrectomy the next day because of recurrent hæmorrhage

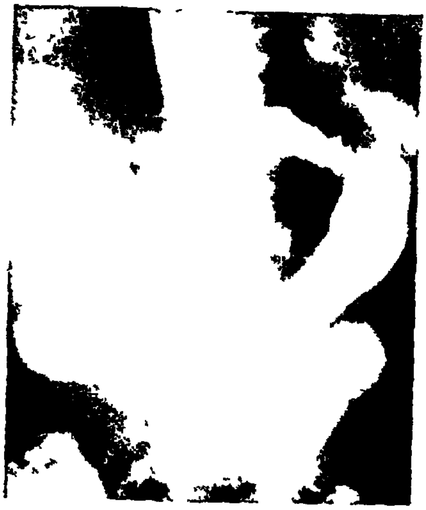

Fig 2—Ward barium-meal film of a man, aged 61, admitted because of recent hæmatemesis

Note arrowing of proximal stomach and infiltration of lower œsophagus by carcinoma

Fig 3—Ward barium-meal examination of a man, aged 24, with melæna

Note deformed duodenal cap containing an ulcer crater

Familiarity with the technique makes for more rapid examination and fewer failures

The details of the procedure should first be explained to the patient so as to allay his anxieties and enlist his cooperation This is the more important when he is drowsy from the effects of recent premedication for gastroscopy Food and fluids are withheld for only two hours preceding the examination The patient wears a close-fitting gown with few tapes, and lies on a cloth-covered board, about 26 × 14 in, since sagging of the normal hospital mattress makes accurate positioning impossible He then drinks 4 oz of barium suspension and is immediately placed in the right lateral position with a 12 × 10 in cassette and grid between him and the board An exposure is made in this position, followed as rapidly as possible by further films in the right-anterior-oblique, right-posterior-oblique, and anteroposterior projections

The portable X-ray machine used for this bedside examination has an output of 30 mA at 85 kVp, and exposure times vary from one to two seconds, depending on the build of the patient and the projection employed Fast films and screens, and a cone that just covers the film at a focal-film distance of 30 in, are used

Results

In the twelve months from November, 1958, 183 patients were admitted to the gastroenterological unit at the Central Middlesex Hospital because of hæmatemesis and/or melæna 150 patients were investigated by early barium-meal examination, and 33 patients were excluded 10 of these (of whom 2 died, aged eighty-three and eighty-four years) were old, feeble, and uncooperative, 4 died within a few hours of admission, and 5 underwent immediate emergency gastrectomy (with 2 deaths) 14 patients were not investigated for reasons outside our control, none of these died

In the other 150 patients the final diagnosis of the cause of bleeding was made at a second barium-meal examination performed in the X-ray department after hæmorrhage had stopped, at operation, or at necropsy The assumed cause of bleeding and the criteria employed for final diagnosis are shown in table I

Table II summarises the results obtained by early ward barium-meal examination in these 150 patients during the acute stages of bleeding

In 16 patients the early radiological diagnosis of chronic gastric ulcer was correct in 12—an accuracy of prediction of 75% The presence of chronic duodenal ulcer was accurately forecast in 52 of 54 patients (96%) where the diagnosis was made by early radiography Of 72 patients in whom ward barium-meal investigation showed no lesion, 53 (73%) were finally considered to have bled from acute ulcers In both patients admitted after hæmatemesis from gastric carcinoma, in 2 patients bleeding from œsophageal varices, and in 3 of 4 patients with hæmorrhage from œsophageal hiatus hernia, the responsible lesion was correctly identified by early barium-meal examination

These results indicate that in most patients information of diagnostic value is provided by this bedside investigation The overall accuracy of the method in 150 patients examined during the acute stages of bleeding was 83%, and the successful recognition of duodenal lesions was particularly impressive Very little misleading or incorrect information was obtained from early X-ray examination

TABLE I—DIAGNOSTIC CRITERIA IN THE PATIENTS STUDIED

Diagnosis	No of patients	Operation	Final barium-meal	Necropsy
Chronic gastric ulcer	20	5	15	0
Chronic duodenal ulcer	61	8	53	0
Acute ulcer	60	3	55	2
Carcinoma of stomach	2	2	0	0
Œsophageal varices	3	1	2	0
Hiatus hernia	4	0	4	0
Total	150	19	129	2

TABLE II—ACCURACY OF PREDICTION OF FINAL DIAGNOSIS BY EARLY BARIUM-MEAL EXAMINATION

Early radiological diagnosis	No of patients	Correct	Incorrect	% accuracy
Chronic gastric ulcer	16	12	4	75
Chronic duodenal ulcer	54	52	2	96
Acute ulcer	72	53	19	73
Carcinoma of stomach	2	2	0	100
Œsophageal varices	2	2	0	100
Hiatus hernia	4	3	1	75
Total	150	124	26	83

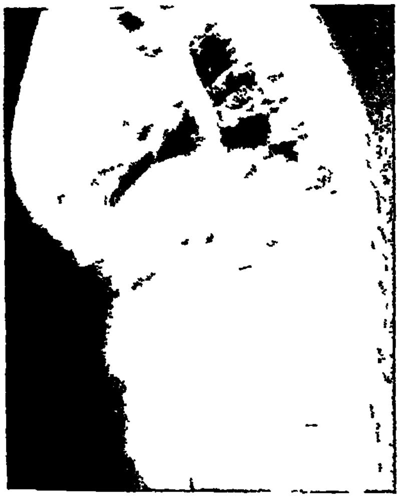

Fig 4—Ward barium-meal film of a woman, aged 44, admitted because of hæmatemesis and melæna
Note extensive œsophageal varices

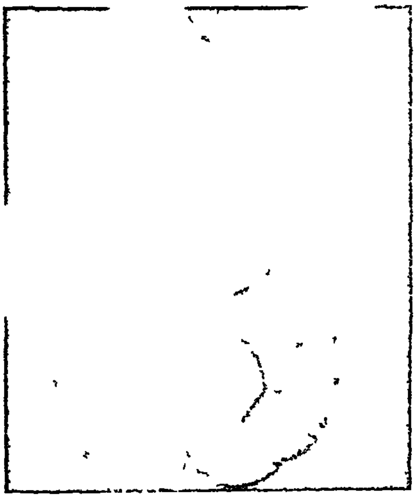

Fig 5—Ward barium-meal examination of a woman, aged 72, with hæmatemesis
Note large paraœsophageal hiatus hernia

Table III shows that failure of the method was more often due to inability to recognise the responsible lesion (in 19 cases among 90 patients bleeding from causes other than acute lesions) than to false information about the cause of illness (which happened only 7 times in the 150 patients studied)

Figs 1, 2, and 3 are photographs of X-ray films of lesions of the stomach and duodenum taken with the portable X-ray apparatus Satisfactory films of the œsophagus are more difficult to obtain at the bedside, but fig 4 illustrates the successful recognition of œsophageal varices Fig 5 shows an œsophageal hiatus hernia in a patient examined by this technique in whom no other cause for hæmatemesis could be found.

If a lesion is suspected in the lower œsophagus the radiologist should be told before the examination is made Œsophageal lesions are best demonstrated by the use of a thick barium paste, with films taken in the lateral projection

No complications have been encountered in this study In no case has further bleeding been attributed to the method of examination, which imposes a negligible disturbance on the patient, and the brief period of fasting causes neither hardship nor risk Barium did not cause intestinal obstruction in those patients in whom radiological examination shortly preceded emergency partial gastrectomy In no patient did the barium fail to pass beyond the pylorus at the time of the first exposure

Discussion

The results of ward barium-meal examination confirm its safety in the acute stages of hæmatemesis From every point of view it is preferable to subjecting the patient to the dangers and disturbance of a journey to the X-ray department, and to the potential hazards of manipulation and compression under screen control, neither is the work of the X-ray department disrupted by the unscheduled examination of acutely ill patients Moreover the accuracy of diagnosis in recent bleeding compares favourably with that of examination in the X-ray department The short period of starvation that precedes the ward investigation does not seriously conflict with the demands of early feeding, and intravenous therapy can be continued undisturbed where necessary

TABLE III—DIAGNOSTIC FAILURES OF EARLY BARIUM-MEAL EXAMINATION

Final diagnosis	No of patients	Les on seen	Lesion not seen	In-correct	% accuracy
Chronic gastric ulcer	20	12	8	0	60
Chronic duodenal ulcer	61	52	9	0	85
Acute lesion	60		53	7	88
Carcinoma of stomach	2	2	0	0	100
Œsophageal varices	3	2	0	0	66
Hiatus hernia	4	3	1	0	75

We have noted that gastric emptying invariably starts immediately after the patient has drunk the barium This contrasts with the delay in emptying often observed in the same patient when examined later in the X-ray department after bleeding has stopped Absence of anxiety may explain the difference, but we cannot exclude the effect of premedication from previous gastroscopy Whatever the cause, the result is that adequate films of the duodenal cap can usually be obtained The right lateral film, which demonstrates the anterior and posterior walls of the duodenal cap, is most useful in revealing a duodenal lesion in cases of recent hæmatemesis because bleeding is most likely from ulcers situated on the posterior wall in the vicinity of the superior pancreaticoduodenal artery The oblique and anteroposterior projections are most valuable for recognising gastric lesions The demonstration of œsophageal lesions requires the use of a thick barium paste and a lateral projection

In the majority of patients admitted after hæmatemesis a ward barium-meal examination can be accepted as a perfectly satisfactory alternative to later radiological examination In most hospitals barium-meal investigation of these patients is delayed for two weeks or more, until full recovery can be assumed In our opinion ward barium-meal examination can safely replace the later conventional examination in the department, except in the small number of cases where doubt as to the cause of bleeding still exists, or the nature of the lesion demands follow-up Probably also, unless gastroscopy be undertaken routinely in hæmatemesis, it would be a wise precaution to re-X-ray those patients in whom ward barium-meal examination shows no lesion Much greater definition has been lent to this " radiologically negative " group by combining early X-ray examination with gastroscopy and studies of acid secretion in the acute stages of bleeding, thus we were able to demonstrate acute ulcers by gastroscopy in more than half of this group (Chandler et al. 1960)

Though we have come to regard a coarse mucosal pattern as suggestive of a duodenal lesion, we have refrained from a radiological diagnosis of gastritis, and we should also hesitate to equate normal radiological findings with a diagnosis of acute ulcer unless further support can be obtained from other investigations The acute-lesion group requires further evidence from gastroscopy or from achlorhydria on hourly gastric aspiration for its confident definition, and in our experience the earlier use of gastroscopy after hæmatemesis has led to an increasing number of acute lesions being observed If the diagnosis of acute ulcer in such patients is based solely on negative radiological findings from ward barium-meal investigation, then a second examination in the X-ray department is desirable when hæmorrhage has ceased Within these limits early radiological investigation in hæmatemesis is of great diagnostic value

The procedure has important practical applications in the management of the patient bleeding from an unknown lesion in the upper gastrointestinal tract Surgical treatment is known to offer the best prospect for survival among older patients with chronic peptic ulcers who bleed again after admission to hospital Ward barium-meal examination has proved both safe and informative, and the early definition of the chronic lesion which its use provides greatly facilitates the often difficult choice between operative and conservative treatment The optimum time for surgical intervention in hæmatemesis lies within the first forty-eight hours after admission to hospital (Gordon-Taylor 1935), and chronic gastric ulcer is a particularly strong indication for operation when bleeding recurs The adoption of a radiological investigation whereby early diagnosis of the cause of bleeding can be achieved in most patients enables correct treatment to be applied at a stage of illness when delay in seeking surgical aid is too often fatal

The benefits of a vigorous diagnostic policy in the acute stages of hæmatemesis are shown not only by a favourable effect on mortality (Chandler et al 1960) but also by a *reduction in the length of the patients' stay in hospital* With early investigation there is no reason why the patient whose recovery is uncomplicated should be kept in hospital for conventional barium-meal examination in the X-ray department There is good evidence that patients who are mobilised as soon as massive hæmorrhage has ceased recover as quickly and completely as patients in whom rest in bed is enforced (Pollard and Summerskill 1960) In most cases ward barium-meal investigation renders a second examination in the X-ray department unnecessary, and there is little doubt that, encouraged by knowledge of the cause of bleeding reached shortly after admission, and in the presence of satisfactory clinical progress, the physician can best serve the interests of the patient by allowing early ambulation The practical advantages of such a policy in preventing the complications of recumbency are obvious, and the social and economic benefits of the patient's earlier discharge home, and his earlier return to work, are considerable

Summary

A method of barium-meal examination in the ward is described This can be performed in any hospital possessing a portable X-ray unit of average output.

150 patients, admitted with hæmatemesis or melæna, have been investigated by this technique in the acute stage of bleeding In 83% the cause of bleeding was correctly diagnosed, and the method was of particular value in the recognition of duodenal lesions

The procedure helps in the choice between operative and conservative treatment

We are grateful to Dr F Avery Jones and Dr T D Kellock for permission to study their patients, and to Dr Frank Pygott of the department of radiology for his criticism and assistance

References at foot of next column

CALCIUM DEPRIVATION IN HYPOPARATHYROIDISM

A METHOD OF DIAGNOSIS USING SODIUM PHYTATE

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An animal deprived of calcium maintains a normal level of calcium in the body fluids (Ham et al 1940), and even if calcium is very rapidly removed from the circulating blood the concentration of the ion is immediately restored by calcium released from bone (Hastings and Huggins 1933, Copp 1957) Patt and Luckhardt (1942) showed that when parathyroid glands were perfused with fluids deficient in calcium their secretion increased Parathyroid hormone acts on bone (Neuman and Neuman 1958), and in calcium deficiency it is likely that calcium is released from bone through an increase in parathyroid secretion. Parathyroidectomised animals fail to maintain their plasma-calcium concentration (plasma-[Ca])

There are very few studies of calcium deprivation in man

Spencer et al (1952) gave patients intravenous infusions of ethylenediamine-tetra-acetic acid (E D T A), a chelating agent which combines with calcium to form a non-ionised complex (*Lancet* 1955) During the infusion the plasma-[Ca++] fell, but the level rapidly returned to normal when the infusion was stopped The plasma-[Ca] also remains within normal limits if sodium phytate is given to prevent the intestinal absorption of calcium Phytic acid is the "anticalcifying factor" of cereals, it probably has the composition of inositol hexaphosphate, and it binds calcium in an insoluble complex (Mellanby 1949) Henneman et al (1956, 1958) gave, to forty-one patients with renal stones, sodium phytate 9 g daily and a diet containing very little calcium The fæcal excretion of calcium increased by 90–250 mg daily and the urinary excretion of calcium fell Phosphorus derived from the hydrolysis of phytate was absorbed, and the urinary excretion of phosphorus increased The plasma-[Ca] apparently hardly changed

To investigate the role of the parathyroid glands in the normal response to calcium deprivation, we gave sodium phytate to patients with parathyroid deficiency

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The results led us to extend the investigation to patients in whom the possibility of parathyroid insufficiency could only be suspected, in this way we were able to show that there is a condition of partial parathyroid insufficiency, which Kramer had postulated in 1936

The Investigation

Normal Plasma Values

Normal values for the plasma-[Ca] and plasma-inorganic-phosphate (plasma-[P]) were established on a strictly random sample of eighty-two women from the Rhondda fach

The range of plasma-[Ca] in the normal women was 8 9–10 8 mg per 100 ml, mean 9 72, S D ±0 37 mg The range of plasma-[P] was 2 4–4 7 mg per 100 ml, mean 3 5, S D ±0 75 mg

Methods

The patients took a diet containing 140–170 mg of calcium daily, and sodium phytate 9 g daily in divided doses In most cases the low-calcium diet was begun 2 or more days before the phytate was started, and phytate was given for at least 5 days, but in three of the later experiments phytate was given for only 3 days

Plasma and urine were analysed for calcium (Kramer and Tisdall 1921, Shohl and Pedley 1922) and phosphate (Gomori 1942)

Patients

The patients were selected from those being followed after thyroidectomy There were three groups

1 Three patients (cases 1–3) with established parathyroid insufficiency, who required treatment to maintain a normal plasma-[Ca] and freedom from tetany

2 Two patients (cases 4 and 5) who, after operation, had had tetany or other symptoms of hypoparathyroidism, but who had apparently recovered and did not require treatment for tetany

3 Nine patients (cases 6–14) who had not had clinical evidence of parathyroid insufficiency after operation, but whose plasma-[Ca] was at times less than the arbitrarily selected value of 9 3 mg per 100 ml.

In addition control observations were made on three patients who had not undergone thyroidectomy, and who had no evidence of parathyroid deficiency

Patients in Group 1

CASE 1, aged 49, had a partial thyroidectomy for thyrotoxicosis in July, 1956 The wound was infected and a sinus persisted until March, 1957 She had tetany immediately after operation, and again in January, 1957 Her plasma-[Ca] was then 6 mg per 100 ml Her symptoms remitted with calcium lactate 15 g daily and calciferol 5 mg daily, and she took this treatment intermittently When she was admitted to hospital for the experimental study she had been having calcium but not calciferol Her plasma-[Ca] was 8 5 and her plasma-[P] 4 6 mg per 100 ml

CASE 2, aged 29, had a subtotal thyroidectomy for thyrotoxicosis in December, 1954 She had tetany 6 days after operation, and for 4 months she had cramps and paræsthesiæ, but she had no later symptoms of tetany although she was not having any treatment Her plasma-[Ca] immediately after operation was 7 0 mg per 100 ml and it subsequently remained at about that level At the time of our study it was 8 2 mg per 100 ml, and the plasma-[P] was 4 5 mg per 100 ml She had no symptoms other than paræsthesiæ in the legs brought on by kneeling

CASE 3, aged 39, had a subtotal thyroidectomy for a diffuse nodular goitre in February, 1957 She had tetany for 4 days after operation and had to be given calcium intravenously A week later her serum-[Ca] was 6 4 mg per 100 ml She was treated with small doses of calcium lactate—3 g daily, equivalent to 0 6 g calcium daily—and the serum-[Ca] rose to 8 0–9 1 mg per 100 ml The plasma-[P] was 3 7–4 5 mg per 100 ml With this treatment she continued to have occasional paræsthesiæ and cramps in the arms

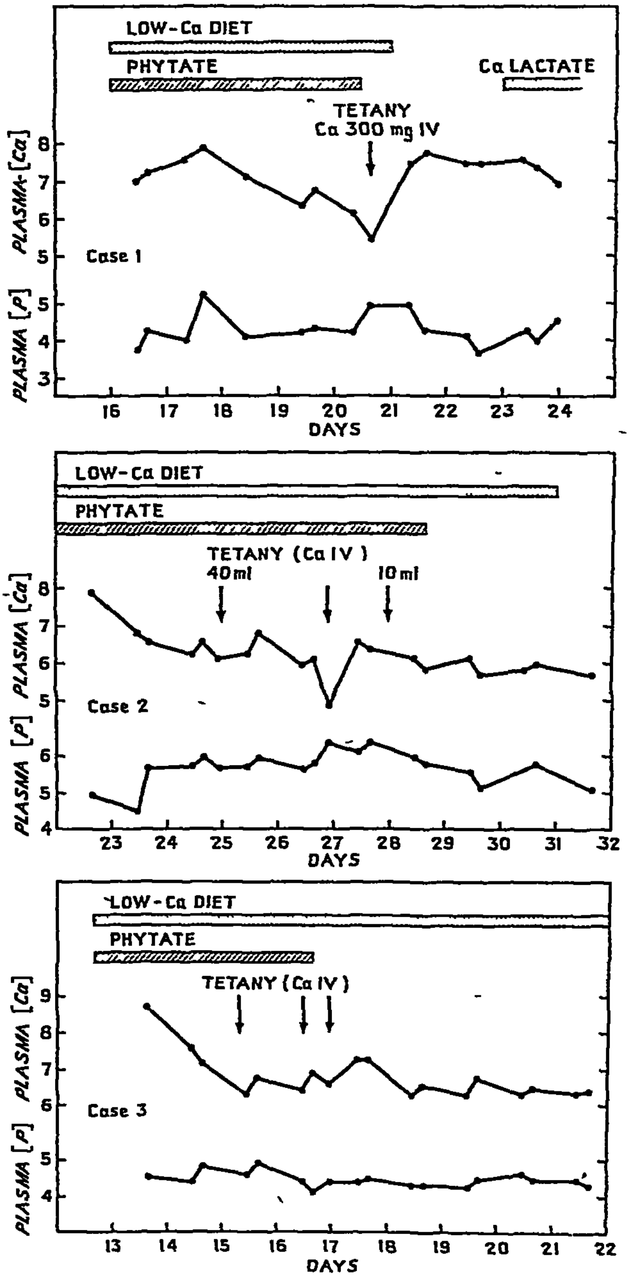
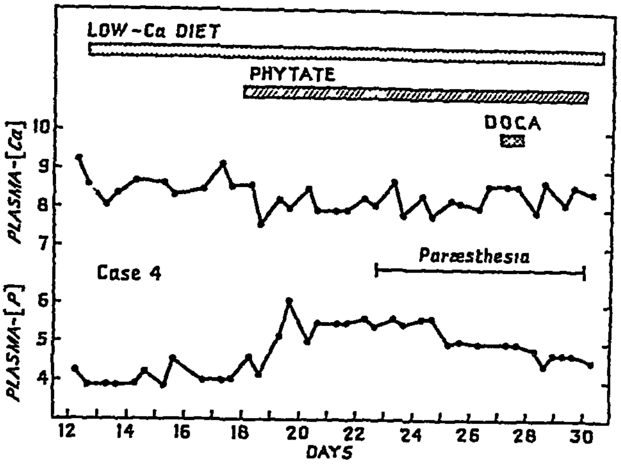


Fig 1—Changes in the plasma [Ca] and [P] in the three patients of group 1, with hypoparathyroidism

Patients in Group 2

CASE 4, aged 56, had a partial thyroidectomy for thyrotoxicosis in August, 1958 She had paræsthesiæ for 10 weeks after operation but no tetany When she was seen 8 months later her plasma-[Ca] was found to be in successive weeks 8 9, 9 3, and 9 2 mg per 100 ml She had minor symptoms which had been attributed to an anxiety state, but she was otherwise well.

CASE 5, aged 44, had had a subtotal thyroidectomy in 1939 and again in 1957 for thyrotoxicosis She had an attack of tetany after the first operation, but no further symptoms of parathyroid insufficiency until after the second operation, and



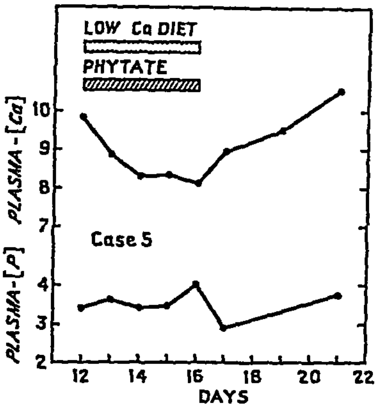


Fig 2—Changes in the plasma [Ca] and [P] in the two patients of group 2, without symptoms of hypoparathyroidism

then she had only paræsthesia, numbness, and cramps in the feet These symptoms have persisted, and she complains of feeling tense At follow-up her plasma-[Ca] was 9·0 mg per 100 ml

Patients in Group 3

The main clinical features, and the values for the plasma-[Ca] of these patients, are shown in the table They all had a normal plasma-[P] None had had tetany after operation, but some had had cramps or paræsthesiæ at other times

Results

Plasma Values

Determinations on the plasma were made daily, but the results are reported only in summary form

The normal response—In the three control subjects who had the low-calcium diet and sodium phytate the plasma-[Ca] and [P] remained within normal limits These results accord with the data of Henneman et al (1956, 1958)

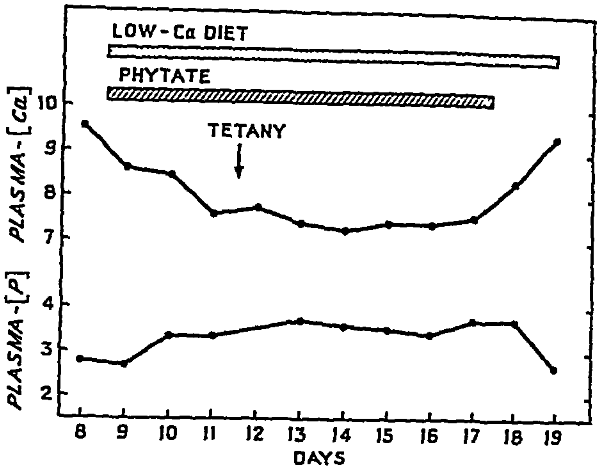


Fig 3—Changes in the plasma [Ca] and [P] in case 6, without previous evidence of hypoparathyroidism

Patients in group 1—Preliminary observations on cases 1–3 with established hypoparathyroidism showed that when their treatment with calcium was stopped for 3 weeks they suffered no serious effects, only one patient had any symptoms, and these were mild The plasma-[Ca] fell by less than 1 mg per 100 ml

Fig 1 shows what happened when phytate was given The plasma-[Ca] rapidly fell The plasma-[P] increased, but this change did not correlate with the changes in [Ca] and may have been the result of increased intake of phosphorus derived from phytate Within 1–3 days the patients had tetany The spasms could be controlled with intravenous injections of calcium gluconate, but otherwise the plasma-[Ca] remained abnormally low as long as the patients continued their low-calcium diet This was so even if the phytate was stopped

Patients in group 2—Cases 4 and 5 had had some evidence of hypoparathyroidism after operation, but they had apparently recovered Yet in both these patients the plasma-[Ca] fell to abnormally low levels with phytate (fig 2) The maximum change was achieved in 3 days, the fall in plasma-[Ca] did not produce tetany

Patients in group 3—The criterion for the selection of cases 6–14 was that their plasma-[Ca] was less than

THE PATIENTS WITHOUT EVIDENCE OF HYPOPARATHYROIDISM (GROUP 3)

Case no	Age (yr)	Date of operation	Plasma-[Ca] (mg per 100 ml)	Plasma-protein (g per 100 ml)	Symptoms	Lowest [Ca] after phytate (mg per 100 ml)
6	43	1956	8·9–9·5	7·4	Tiredness	7·6 (day 3) 7·2 (day 6)
7	51	1931 1946 1952	8·9	7·3	Lethargy	8·1 (day 2)
8	43	1955	9·2	7·2	Cramps and abdominal colic	8·1 (day 2)
9	43	1956	8·8–9·3	6·6	Muscular cramps	9·2 (day 5)
10	26	1952 1953 1955	9·2–9·4		Carpopedal spasms during only pregnancy in 1958, paræsthesiæ occasionally	8·6 (day 3)
11	60	1933	8·9–9·5	6·3	Paræsthesiæ and recent cramps	9·3 (day 5)
12	34	1954	9·0	5·8	Attacks of falling without loss of consciousness, cramps and paræsthesiæ	8·4 (day 4)
13	42	1953	9·0–10·5	7·0	None	8·6 (day 3)
14	35	19-4 1957	9·1	7·2	Paræsthesiæ beginning 12 months after second operation	8·5 (day 3)

9·3 mg per 100 ml—i.e., at about the lower limit of normal. The nine patients in this group inevitably include some with normal parathyroid function, but, as may be seen from the table, only two of them maintained their plasma-[Ca] above 9 mg per 100 ml when they were given phytate. In four the plasma-[Ca] fell to 8·4–8·6 mg per 100 ml. While we look upon this as an abnormal response it is unlikely to be of great clinical import. In the other three patients the plasma-[Ca] fell to 8·1, 8·1, and 7·2 mg per 100 ml, results that are clearly abnormal (fig. 3). In the patients who were followed the plasma-[Ca] returned to normal in 1 or 2 days after the phytate was stopped.

Urinary Excretion of Calcium and Phosphorus

Urinary calcium and phosphorus was estimated in all the group-3 patients except two. This did not contribute any information of value, and the findings need only be summarised briefly.

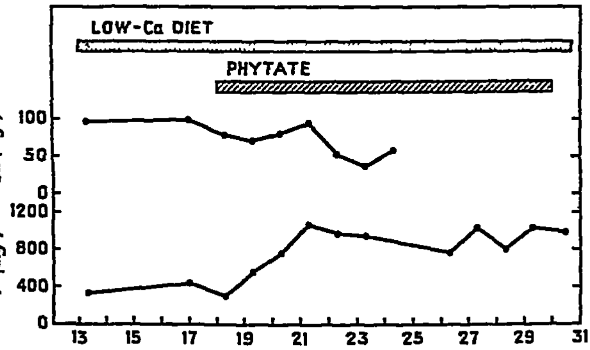


Fig. 4—The changes in the urinary excretion per 24 hours of calcium and phosphorus in case 4.

The urinary excretion of calcium fell to 6–40 mg daily, and the fall did not correlate with the fall in plasma-[Ca]. The urinary excretion of phosphorus usually increased, in some cases to as much as 2 g daily, but in two patients of group 1 there was no increase. This presumably means the phytate was not hydrolysed in the gut. Fig. 4 illustrates the usual type of response.

Discussion

The results show that the ability to maintain a normal plasma-[Ca] in the face of deprivation of calcium depends on normal parathyroid function. They also reveal that after thyroidectomy a patient may have sufficient parathyroid tissue to maintain a normal plasma-[Ca] under ordinary circumstances, but insufficient to respond to the test of calcium deprivation. The possibility of partial parathyroid insufficiency (Kramer 1936) is thus confirmed. Kaiser and Ponsold (1959) recently arrived at the same conclusion from a study of the ability of patients to recover from hypocalcæmia produced by an infusion of E.D.T.A.

The exact clinical importance of partial parathyroid insufficiency remains to be determined, though it is already obvious to us that unrecognised parathyroid insufficiency can account for much disability in patients who have had a thyroidectomy. If they happen not to have frank tetany they are liable to be thought neurotic, and even with tetany a diagnosis of neurosis is likely to be made if the serum-calcium is not low at the time of examination.

In patients who have had a thyroidectomy, symptoms such as lassitude, abdominal cramps, eczema, and various psychological disorders including depression and the so-called premenstrual tension syndrome, may be due to hypoparathyroidism (Kramer 1936, Reinberg and Sidi 1959). In hypoparathyroidism a fall in plasma-[Ca] is not a constant finding, but it appears that a low-calcium diet with the addition of phytate 9 g daily for 3 days will cause the plasma-[Ca] to fall abnormally low, thus making the diagnosis clear even in patients whose parathyroid insufficiency is only partial.

Our results are in some ways unexpected. Firstly, the number of patients found to have parathyroid insufficiency was surprisingly large. Except for the women in group 1 they were all drawn from an unselected group of forty-six women who had had a thyroidectomy, in the practice of one of us (R. H. D.). At least five of those tested did not respond normally to calcium deprivation. This suggests that damage to the parathyroid glands must be common, although accidental removal of the parathyroids during thyroidectomy must now be uncommon. The glands are supplied by the inferior thyroid artery, and presumably they are damaged by a reduction in their blood-supply.

But—and this brings us to the second unexpected feature—the glands normally can hypertrophy: why do they not do so when they have been damaged during thyroidectomy? Two explanations may be offered: (1) that damage to the vascular supply limits hypertrophy, and (2) that the glands in these cases have in fact become sufficient for ordinary needs, their inadequacy being revealed only by the special strain of calcium deprivation.

Summary

Patients were given sodium phytate and a diet low in calcium, and were thus deprived of calcium. In those with normal parathyroid function the plasma-calcium (plasma-[Ca]) remained normal.

In patients with hypoparathyroidism the plasma-[Ca] fell sharply, showing that the normal response depends on parathyroid function.

A number of patients who had had a thyroidectomy without evidence of parathyroid insufficiency showed an abnormal fall in plasma-[Ca]. It is suggested that they had partial parathyroid insufficiency, this condition may be fairly common.

We are indebted to Prof. A. L. Cochrane and Dr. Peter Oldham for their help in enabling us to study the people of the Rhondda fach, to Mrs. M. Lewis and Miss M. Hopkins for technical assistance, and to Messrs. E. R. Squibb & Sons and Ciba Laboratories, Ltd., for supplying sodium phytate. We are grateful to Prof. H. Scarborough for his help and encouragement at all stages of this work.

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MUCOVISCIDOSIS AS A FACTOR IN CHRONIC LUNG DISEASE IN ADULTS

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CHRONIC lung infection, once regarded as a frequent complication of mucoviscidosis, is now accepted as an inherent part of this condition (Andersen 1958), and it may present with slight or no pancreatic involvement In this widened concept of the disease the diagnosis can now be made by the finding of raised sweat-electrolyte concentrations (di Sant'Agnese et al 1953, di Sant'Agnese 1956a), and it no longer depends on estimations of pancreatic enzyme

Our interest in the problem goes back to May, 1958, when we saw a girl of 5, who had, for 3 years, had recurrent staphylococcal lung infections leading to pulmonary fibrosis with dyspnœa, cyanosis, and much finger clubbing There was no clinical or laboratory evidence of pancreatic deficiency, her sweat-electrolyte levels were raised (chloride 83 mEq per litre and sodium 83 mEq), she had a positive fingerprint test (Shwachman and Gahm 1956) indicating a high sweat-chloride content, and two of her four close relatives tested were also finger-print-positive This appeared, therefore, to be an example of genetically determined mucoviscidosis in which lung disease, and not pancreatic impairment, was the predominant feature

We then decided to examine the possibility that a proportion of cases of chronic non-tuberculous lung disease, in adults as well as in children, might be forms of mucoviscidosis

Patients and Methods

Our series so far comprises forty-eight patients (twenty-three male, twenty-five female), and eighteen healthy controls (nine male, nine female) Thirty-three patients were adults, aged 13–60 (mean 32), and the rest were children, aged 4–12 years (mean 8) Eleven controls were adults, aged 13–45 (mean 29), and seven were children, aged 5–11 years (mean 9)

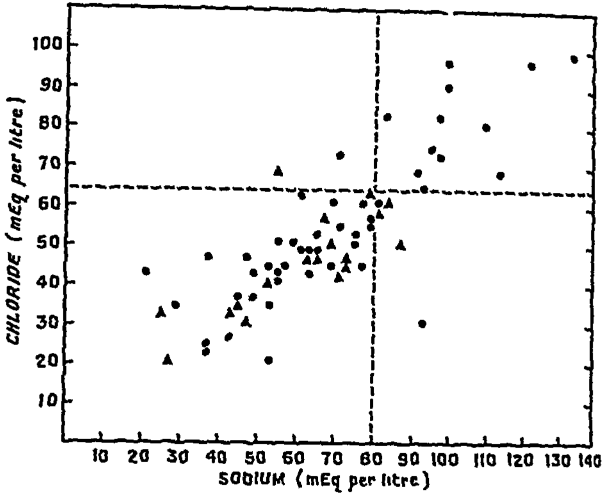
The patients chosen for investigation were attending the Reading chest clinic under such diagnostic labels as chronic bronchitis, emphysema, asthma, and bronchiectasis

The criteria for selection were recurrent or chronic lung disease of some years' standing, absence of tuberculosis, and, in many cases but not all, a family history of similar non-tuberculous lung disease The controls were eleven healthy adults without personal or family history of respiratory illness, and seven children convalescing from primary tuberculous infection but otherwise free from lung disease

Sodium and chloride levels were estimated in the sweat collected by the plastic-bag method (Tarnoky 1958) in all sixty-six cases Fingerprint-chloride tests (Shwachman and Gahm 1956) were done on eighteen patients and sixteen of their close relatives Fæcal trypsin (Tarnoky 1958) was estimated in ten children Bronchography was done in thirty-two cases In addition, corticotrophin tests (Prout and Snaith 1958) were performed in four children with mucoviscidosis, and their urinary 17-ketosteroid (Norymberski et al 1953) and 17-hydroxycorticosteroid (Appleby et al 1955) outputs were measured

Results

The distribution of sweat-electrolyte levels is shown in the figure



Sweat-electrolyte levels of forty-eight patients with chronic non tuberculous lung disease (circles) and of eighteen normal controls (triangles)

Our normal limits (marked in broken lines) are higher than the 60 mEq per litre of chloride and 70 mEq of sodium recently quoted (*Lancet* 1960, Bohn et al 1959, Koch 1960) and are nearer 65 mEq for chloride and 80 mEq for sodium A well-differentiated group of abnormally high values appears at the top right-hand corner, this group comprises twelve patients, eleven of whom are adults, with sweat values for chloride of 66–99 mEq per litre (mean 82) and for sodium 83–134 mEq per litre (mean 103) The eleven adults (seven men, four women) were aged 14–60 (mean 34)

One other case was suggestive A boy of 11 years had sweat-chloride of 62 mEq per litre, and sweat-sodium of 78 mEq, and a positive fingerprint test, his father, who had chronic bronchitis and a duodenal ulcer, had sweat-chloride of 90 mEq, and sweat-sodium of 99 mEq One only of the controls, a healthy man aged 26 with no history of lung disease, had a raised sweat-chloride level of 70 mEq per litre

The electrolyte levels in our abnormal group are lower than those quoted in the United States (di Sant'Agnese 1956b) for children with more acute pancreatic forms of the disease, but they agree with those published by Bohn et al (1959) and Koch (1960) who, like us, studied adults There was no striking difference between the sweat-electrolyte levels of our adults and children, but in twelve younger children (aged 3 months to 3 years), who were not part of this series and in whom the diagnosis of mucoviscidosis was excluded, the values were 1–39 mEq of chloride (mean 18) and 5–35 mEq of sodium (mean 22) per litre These results are even lower than those of Webb et al (1957), and agree with the finding of lower normal levels in early childhood reported by Dancis et al (1957)

Fingerprint tests gave a number of false negative results, perhaps owing to slow rates of sweating in out-patient departments All the fæcal trypsin estimations in the children of this series were normal

The 32 bronchograms (24 bilateral) were done in an attempt to correlate sweat-electrolyte levels with the severity of lung changes 4 bronchograms were classified as normal, 4 as doubtful, 14 as abnormal, and 10 as grossly abnormal No distinct abnormality was seen, the extent varied from minor irregularities of bronchial outline to gross bronchiectasis Of the twelve patients with abnormally high sweat electrolytes five had grossly abnormal bronchograms, five had abnormal ones, one was doubtful, and one was normal—this small group accounting for a high proportion of abnormal bronchograms

RESULTS OF CORTICOTROPHIN TESTS ON CHILDREN WITH MUCOVISCIDOSIS

Patient	Sex	Age (yr)	Sweat electrolytes (mEq per litre)		17-ketosteroids (mg per ml. of 24-hr urine-vol)		17-hydroxy-corticosteroids (mg per ml. of 24-hr urine-vol.)	
			Sodium	Chloride	Before corticotrophin	After corticotrophin	Before corticotrophin	After corticotrophin
B P	M	7	73	80	1 0/315	1·6/875	1 9/315	10 3/875
N F	F	5	83	83	0 4/105	1 7/400	1 2/105	9 8/400
C. R.	M	2¹/	77	120	0 6/175	2·0/720	0 7/175	8 2/720
M C.*	M	1¹/₂	152	144	0 7/80	0 8/100	1 4/80	1 3/100

* Diagnosed in 1957 as mucoviscidosis Sister died when 6 months old, mucoviscidosis confirmed at necropsy Readmitted in 1958 for corticotrophin test but had tonsillitis on the 4th day of test.

di Sant'Agnese and his colleagues (1953, 1956b, 1958) have stated that adrenal disease is not a factor in mucoviscidosis, though the high sodium content of both sweat and saliva is suggestive of adrenocortical insufficiency Corticotrophin tests were performed in four children (three of them not part of the present series) who had been diagnosed as cases of mucoviscidosis

They were given 20 mg corticotrophin gel intramuscularly twice daily for 4 days, and their urinary 17-ketosteroids and 17-hydroxycorticosteroids were determined on the day before the test and on the 4th day The results are given in the table. Three of the four cases had normal adrenocortical function, while in the fourth acute tonsillitis interfered with the results of the test.

Bohn et al (1959) and Gochberg and Cooke (1956) have done repeated sweat-electrolyte determinations during deoxycortone-loading tests (Conn 1949) and their results, like ours, showed no evidence of adrenal deficiency

Discussion

So long as the diagnosis of mucoviscidosis depended on demonstrating depressed pancreatic function, incomplete forms of the disease with respiratory infection but normal pancreatic activity were missed The introduction of sweat-electrolyte measurements enabled us to study such cases and to explore the wide field of chronic lung disease The main difficulty has been the selection of cases, here we had nothing to guide us except the known genetic nature of the disorder, always bearing in mind that a family history of chronic lung disease could be due to environmental rather than hereditary causes Given these difficulties, we think that finding twelve suggestive cases in a miscellaneous group of forty-eight, and in particular eleven cases among thirty-three adults, warrants further study

Three of our eleven adults with abnormal sweat electrolytes had peptic ulcers, but until recently we have not specifically pursued this point, the significance of which has become apparent since Bohn et al (1959) reported seventeen cases of peptic ulcer in forty-one adults with mucoviscidosis These observations recall earlier comment on the high incidence of gastric and duodenal ulcers in bronchitic patients (Latts et al 1956)

Summary

Eleven of thirty-three adults, and one of fifteen children (with a further suggestive result in a boy of 11), attending a chest clinic and previously diagnosed as having bronchitis, emphysema, asthma, or bronchiectasis, had abnormally high sweat-electrolyte levels consistent with mucoviscidosis

Several relatives of the three patients so far examined also had high sweat-chloride values

A genetically determined mucoviscidosis factor seems likely to be present in a significant proportion of adults with chronic non-tuberculous lung disease

The children not in our series were under the care of Dr J J Kempton, and we are grateful that he referred them for biochemical investigation. We also wish to thank Dr W S Holden of Oxford for many of the bronchograms, and Dr J C. Booth, Dr B D Chalkley, and Dr P K Hammick for their help with sweat-electrolyte tests

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ANTIBIOTIC SENSITIVITY OF STAPHYLOCOCCI FROM NOSES OF VETERINARY SURGEONS AND FARMERS

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Recently Gould (1957, 1958) indicated that the presence of penicillin in the environment is an important reason for the high proportion of penicillin-resistant strains of *Staphylococcus aureus* found in the noses of hospital staff, patients not being treated with penicillin, and workers in penicillin factories

We made a similar survey of strains isolated from the noses of veterinary surgeons, since they handle penicillin frequently, and to a lesser extent other antibiotics Farmers were also examined because they seemed to be the most appropriate control group although they occasionally administer antibiotics to their own animals

Materials and Methods

Within a few hours of collection, nasal swabs were incubated at 37°C for twenty-four hours in 25 ml of Robertson's cooked-meat medium ('Oxoid') to which were added 8 0% sodium chloride and 0 4% sterile bovine serum Subcultures were then made on to milk-agar plates (Mackie and McCartney 1953) These were incubated at 37°C for twenty-four hours and then left at room temperature for a further twenty-four

Wherever possible, 12 staphylococcal colonies which were shown by means of the slide "coagulase" test to produce clumping factor (Duthie 1954) were picked from each plate These strains were purified by replating and then tested for sensitivity to penicillin, tetracyclines, streptomycin, and chloramphenicol (Smith and Crabb 1960) and for the production of penicillinase (Gots 1945), hæmolysin (Elek and Levy 1950) and opacity in egg-yolk medium (Gillespie and Adler 1952)

Results

The results of examining nasal swabs from 200 veterinary surgeons and 200 farmers are shown in the table The carrier-rate of *Staph aureus* was approximately the same in the two groups, but penicillin resistance was about four times commoner among the strains from the veterinary

ANTIBIOTIC-RESISTANT STAPHYLOCOCCI IN NASAL CARRIERS AMONGST 200 VETERINARY SURGEONS AND 200 FARMERS

—	Veterinary surgeons	Farmers
Carriers of *Staph aureus* (%)	34 0	38 0
Carriers whose *Staph aureus* were penicillin-resistant (%)	*88 3 (30 0)*	*21 1 (8 0)*
Carriers whose *Staph aureus* were resistant to tetracyclines, streptomycin, or chloramphenicol (%)	14 7 (5 0)	2 6 (1 0)

The figures in parentheses are the percentages of total veterinary surgeons or farmers

surgeons (88%) than among those from farmers (21%) In one carrier only in each group were both penicillin-sensitive and penicillin-resistant strains isolated, the others appeared to harbour either all penicillin-sensitive or all penicillin-resistant strains

There was no great difference between the degree of penicillin resistance of the resistant strains isolated from the veterinary surgeons and of those isolated from the farmers Of those from the veterinary surgeons, 60% were inhibited by 0 2–1 0 unit of penicillin per ml, 28% by 1 0–10 units per ml, and 12% by 10–25 units per ml All these strains produced penicillinase The strains classed as sensitive were inhibited by less than 0 1 units of penicillin per ml

Strains of *Staph aureus* resistant to antibiotics other than penicillin were found more often in veterinary surgeons (10 persons) than in farmers (2 persons) The strains from 9 of the 10 veterinary surgeons were also penicillin-resistant, those from 4 were resistant to tetracyclines, from 3 to streptomycin, from 1 to tetracyclines and streptomycin, and from 1 to tetracyclines, streptomycin, and chloramphenicol Those from the 10th were tetracycline-resistant The strains from the 2 farmers were also resistant to penicillin, from one to tetracyclines and from the other to streptomycin To inhibit their growth, the tetracycline-resistant strains from veterinary surgeons and farmers required 16–500 µg oxytetracycline hydrochloride per ml, the streptomycin-resistant strains 400 µg streptomycin sulphate per ml, and the chloramphenicol-resistant strain 50 µg chloramphenicol per ml Of the antibiotic-resistant strains isolated from veterinary surgeons, 21% produced β-hæmolysin All produced opacity in egg-yolk medium

Discussion

It is unlikely that the veterinary surgeons had acquired their penicillin-resistant strains of *Staph aureus* from animal patients receiving penicillin The contact between veterinary surgeons—particularly those engaged in agricultural practice—and their patients receiving penicillin is infrequent and brief compared with the contact medical and nursing staffs of hospitals have with theirs Also the resistant strains isolated from the veterinary surgeons, as a group, had characters resembling human rather than animal strains, only a minority of them produced β-hæmolysin (Elek and Levy 1950) and all produced opacity in egg-yolk medium (Adler et al 1953)

There seems little reason to think that the much higher proportion of penicillin-resistant strains in veterinary surgeons was due to the veterinary surgeons having been treated with penicillin more often than the farmers No precise information was obtainable from the farmers, but about 20% of the veterinary surgeons with resistant strains had had some form of penicillin treatment in "the last year or so" Therapy played no part at all in accounting for the 10 veterinary surgeons harbouring strains resistant to the other antibiotics, since none of them had received antibiotic therapy

We must conclude, therefore, that the principal factor in the high incidence of penicillin-resistant strains c *Staph aureus* in the veterinary surgeons was the penicilli in their environment Veterinary surgeons handl penicillin frequently in powder, liquid, and ointment, an the conditions of general veterinary practice are such tha there is much greater opportunity for contamination wit these preparations than there is in a human hospital

Our findings not only support those of Gould (1957 1958) but indicate that penicillin has a very limited valu in the treatment of staphylococcal infections in veterinar surgeons They suggest, too, that this will become tru of other antibiotics unless more stringent precautions an taken when handling these agents during the treatment o animals

Summary

88% of the strains of *Staph aureus* isolated from th noses of veterinary surgeons were penicillin-resistant The corresponding figure for farmers was 21%

The proportion of strains resistant to tetracyclines streptomycin, or chloramphenicol was also higher in th veterinary surgeons (15%) than in the farmers (3%)

The high incidence of resistant strains in the veterinar surgeons is probably related to the fact that they handl antibiotics frequently

We are grateful to Miss Barbara Weeks and Miss Linda Kelly fo their capable technical help and to Dr K C Sellers and Dr R E O Williams for helpful suggestions made during the course of this work

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SICKLE-CELL DISEASE IN PREGNANCY

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THE association of sickle-cell disease and pregnancy has interested obstetricians for many years The first report of pregnancy in sickle-cell anæmia is by Sydenstricker in 1924 In 1931 Yater and Mollari described a case with fatal outcome due to a crisis Kobak et al (1941) made the first detailed survey of the effects of sickle-cell anæmia on pregnancy and concluded that the combination of both conditions was rare, the fœtal and maternal mortality high, and obstetric complications much increased Although most authors have agreed with Kobak et al about the increased maternal and fœtal risks, Anderson and Busby (1949) and Adams et al (1953) reported series with no maternal deaths

It is only since the introduction of filter-paper electro-

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TABLE I—BREAKDOWN OF CASES

Genotype	No of cases	Total no of pregnancies	Maternal deaths	Abortions	Stillbirths	Surviving infants	Average birthweight (present series)	Genotype of parents	Genotype of children
SS	9	17	0	1*	2†	14	5 lb 10 oz.	8 AS	10 AS 1 SS
S"F"	1	5	0	0	0	5	7 lb 8 oz.	AS and A"F"	2 AS 1 A"F" 1 SS 1 S"F"
SC	7	17	0	2*	0	15	6 lb 9 oz		1 AS 7 AC 1 SC 2 SS

* All in previous pregnancies † One stillbirth (case 3) in present series, one in course of previous pregnancy

phoresis of hæmoglobins by Spaet (1953) that the differentiation of sickle-cell anæmia from its variants has become possible in routine hospital practice Series of cases of sickle-cell anæmia published before this date undoubtedly included examples of sickle-cell/hæmoglobin-C disease and sickle-cell thalassæmia In consequence it is difficult to evaluate reports prior to 1954

Abrams (1959) has shown that the possession of the sickle-cell trait does not represent a hazard in pregnancy Smith and Conley (1954) and Edington (1957) have suggested that pregnancy is especially hazardous in sickle-cell/hæmoglobin-C disease Abrams and Schwartz (1959) and Alper et al (1959), on the basis of a few selected cases, concur with this view On the other hand, Sackner et al (1959) suggest that it is only in pregnancy that some patients with sickle-cell/hæmoglobin-C disease have symptoms and that these symptoms are no more frequent or hazardous than in sickle-cell anæmia

In view of these conflicting opinions a report of our own observations may be of interest

The Patients

17 patients with various types of sickle-cell disease were followed through one pregnancy and were delivered at the University College Hospital

With 2 exceptions these deliveries took place during 1957–59 The distribution of cases and the number and outcome of previous pregnancies are shown in table I The clinical and laboratory findings are summarised in tables II and III 9 of the patients had sickle-cell anæmia, 7 had sickle-cell/hæmoglobin-C disease, and 1 (case 10) an unusual combination of a

TABLE II—PERTINENT CLINICAL FINDINGS

No	Age	Parity	Genotype	Jaundice	Joint pains	Leg ulcers	Hepatomegaly	Splenomegaly	Fever	Previous symptoms of S C.D	Comments
1	30	5	SS	++	+(P.P)	+	++	–	+(P.P)	+[2]	Crisis on 4th day P.P First symptoms attributable to sickle-cell anæmia, aged 28 yr
2	26	1	SS	++	+++(P.P)	Scars	+++	–	++(P.P)	+	Jaundice from childhood Joint pains from 18 yr Crisis at 21 and 23 yr
3	22	1	SS	+++	+++	–	?	–	+	+	Emergency admission at 28/52 with joint pains and severe anæmia Intra-uterine death Bone-marrow megaloblastic. Responded to folic acid.
4	26	4	SS	++	–+(P.P)	Scars	+++(P.P)	–	–(P.P)	+	Jaundice with all pregnancies Crisis from 3rd to 6th day
5	20	1	SS	++	+	„	+–+	–	+++	–[1]	Abdominal crisis 36 wk Sudden collapse on 6th day P P Acute cardiac failure. Another crisis 5 weeks later
6	20	1	SS	++	+	+	++	±	++	+	Cæsarean section Stormy post-operative course Three previous admissions, one for arthrodesis right hip
7	21	1	SS	–	±	–	+ to ++	–	+(P.P)	+	Cæsarean section
8	38	1+1	SS	Slight	–	–	–	–	–	–[1]	Episodes of acute dyspnœa and chest pain at 38 wk. Cæsarean section
9	17	1	SS	+++	+	Scars	++	+++	++	+	Crisis at 20 wk. and 34 wk. with severe jaundice Unilateral hæmaturia at 22 wk Evidence of folic acid deficiency at 34 wk.
10	25	5	S+F	–	–	–	–	–	+ (P.P)	–[2]	Fever due to thrombophlebitis on 6th day P.P
11	19	1	SC	+	–	Scars	±	++++	+(P.P)	–	Splenic infarct. 13th day P.P Jaundice and leg ulcer, aged 8 yr
12	19	1+1	SC	–	+(P.P)	–	++	+	+(P.P)	–[2]	Fever and joint pain 4–6th day P.P
13	39	5+1	SC	–	–	–	+++	+++	–	–[2]	No complications
14	23	1	SC	–	–	–	–	+	–	–[2]	No complications
15	32	2	SC	–	–	–	+(P.P)	–	–	–[3]	No complications
16	19	1	SC	–	+	–	+	–	–	–[1]	Slight joint pains at 38 wk.
17	28	4	SC	–	–	–	+	++	–	–[4]	No complications

P.P = post partum. S C.D = sickle-cell disease.

[1] Diagnosis made in course of investigation of anæmia.

[2] Diagnosis made in course of electrophoretic survey (Went 1957)

[3] Diagnosis following routine hæmatological investigation.

[4] Diagnosis as result of family study

TABLE III—MAIN LABORATORY FINDINGS

No	Genotype	Lowest Hb (g. per 100 ml.)	Highest Hb (g. per 100 ml.)	Reticulocytes % (range)	White cells (per c. mm.)	Hb F (% of total Hb)	Bilirubin (mg. per 100 ml.)		Transfusions
							Conjugated	Total	
1	SS	6·7	8·8	9–23	11,000	9	0·5	2·5	Nil
2	SS	6·8‡	8·8	8–15	15,900	5	0·6	1·6	Nil
3	SS	4·1*	9·6†	5*–30	16,000	3	12·0	16·0	2 × 500 ml.
4	SS	7·2	9·7	6–38	10,000	11	0·8	2·3	Nil
5	SS	6·7	9·9†	10–25	15,000	6	0·5	1·1	500 ml.
6	SS	5·8‡	9·1†	0·5†–31	14,000	6	0·7	4·0	500 ml.
7	SS	8·3	9·2	7–8	13,000	5	0·3	0·5	Nil
8	SS	7·3	11·0†	3†–20	10,000	10	0·6	1·3	5 × 500 ml.
9	SS	5·3*	9·1	19–50	10,000	14	0·3	1·6	Nil
10	SF	12·0	13·4	1–3	7000	27	0·3	0·6	Nil
11	SC	7·6	10·1	5–6	6000	2·0	0·5	2·3	Nil
12	SC	10·0	11·5		4000	2·4, 13	0·1	0·6	Nil
13	SC		10·4		5000	1·3, 16, 12			Nil
14	SC	8·6	11·1	3–5	7000	3·9–2·2	0·4	0·8	Nil
15	SC	10·8	11·7	3–7	4000	0·7	0·5	0·8	Nil
16	SC	9·6	10·6	7	11,000	2	0·1	0·3	Nil
17	SC	10·9	12·3	11	5000	1·8	0·3	0·7	Nil

* Folic-acid deficiency † After transfusion ‡ Postpartum hæmorrhage

sickle-cell gene with a thalassæmia-like gene. This case has been described elsewhere (Went and MacIver 1958a). Differentiation between these types of sickle-cell disease was made primarily by hæmoglobin electrophoresis. In case 10 the absence of anæmia and the high percentage of fœtal hæmoglobin pointed to the correct diagnosis which was later confirmed by family studies.

The differentiation of sickle-cell thalassæmia from sickle-cell anæmia is notoriously difficult since both may present an identical pattern on hæmoglobin electrophoresis. In the light of our experience (Went and MacIver 1958b) we are confident that these 9 patients had sickle-cell anæmia with the possible exception of case 9 in whom there was considerable splenomegaly, which is rather unusual in adult sickle-cell anæmia. However, both the mother and the infant of this patient had the sickle-cell trait.

Complications

The most striking complications in sickle-cell disease are acute episodes or crises which may affect the patient in various ways.

Singer et al. (1950) described three types of crisis: hyperhæmolytic, aplastic, and a combination of the two. There is also the well-recognised painful crisis which appears to be due to erythrostasis of sickled red cells (Golding et al. 1959) and is commonly observed in bones, joints, abdomen, and chest. It is usually associated with fever and leucocytosis but not with a significant fall in hæmoglobin. Diggs (1956) has given good evidence that there is *no increased destruction* of red cells in the painful crisis, nor in any other acute episode related to sickle-cell anæmia. Our own experience confirms this view, since in the majority of painful crises which we have seen the hæmoglobin level and reticulocyte count have remained steady. In patients who had an acute episode associated with a low hæmoglobin and reticulocyte level, bone-marrow examination has enabled us to demonstrate either folic-acid deficiency (as in cases 3 and 9) or an aplastic crisis.

Although patients with sickle-cell disease are commonly jaundiced there is considerable individual variation (see table III). Case 6 has been followed over a period of seven years and has constantly had a high level of free bilirubin. At the opposite extreme case 7 has never shown an elevated bilirubin. It seems likely that such marked individual variations may be caused by a varying level of the liver enzyme (glucuronidase) necessary for the conjugation of bilirubin. Sometimes jaundice is of an obstructive type (case 3) but this is usually of short duration and often accompanies an abdominal crisis. The liver may then increase in size, and it is possible that the resultant congestion interferes with the excretion of the large quantities of bilirubin normally produced in sickle-cell anæmia.

An increase in the rate of hæmolysis might be expected to produce a fall in hæmoglobin level, a rise in free bilirubin, and an increased reticulocytosis. We have never observed this combination of circumstances which is required for the diagnosis of a hyperhæmolytic crisis.

Maternal Hazards

The main symptoms of sickle-cell disease and the complications of pregnancy are shown in table II and summarised in table IV.

In *sickle-cell anæmia* moderate to severe exacerbations of the disease were seen in 8 of our 9 patients. These exacerbations were usually painful crises and produced a wide range of symptoms, including apparent pulmonary infarction in case 8 and cardiac failure in case 5.

In case 7 the pregnancy did not appear to influence the severity of the disease, which was mild, and there was no increase in serum-bilirubin throughout the period of observation. In most cases the manifestations of the disease were more frequent and more severe in the puerperium than in the antenatal period. In 2 cases (1 and 2) complications were only observed post partum. The increased incidence of exacerbations during the puerperium has been noted by several authors but the reason for it is not clear. It has been suggested that a crisis may be precipitated both by infection and anæmia but there was no evidence of infection in these patients and there was no significant change in the hæmoglobin levels from those in the antenatal period.

Pre-eclampsia arose in 2 of the 9 cases (2 and 5) of sickle-cell anæmia, but was mild and did not seem to be a major hazard in spite of previous reports (Beacham and Beacham 1950, Margolies 1951). Hæmaturia was seen in 1 patient with sickle-cell anæmia: no reason for this was found and it is considered to be an incidental manifestation of sickle-cell disease. The association of hæmaturia and sickling (including especially the sickle-cell trait) is well recognised (Alleyne and Went 1959).

In *sickle-cell/hæmoglobin-C disease* clinical manifestations attributable to the disease were not striking.

TABLE IV—COMPLICATIONS

Complication	No. of cases		
	SS 9	SC 7	SF 1
Joint pains	7	2 (mild)	
Abdominal crisis	2		
Acute cardiac failure	1		
Splenic infarction		1	
Pulmonary infarction	2		
Cerebral symptoms	1		
Hæmaturia	1		
Thrombophlebitis			1
Pre-eclampsia	2	1	
Folic-acid deficiency	2		
Cæsarean section	3		

Complications were absent in 4 cases Very slight joint pains were noted in case 16 Case 11 had a splenic infarct post partum and case 12 had a mild crisis also post partum Splenomegaly (a common feature in sickle-cell/hæmoglobin-C disease) was noted in 5 cases Scars from healed leg ulcers were seen in only 1 case Again, when symptoms were present in the disease they seemed to occur in the puerperium Mild toxæmia was present in case 15

In case 10 where the unusual combination of an S and an F gene occurred, no complications were seen apart from a postpartum thrombophlebitis

It has been suggested (Duckett and Davies 1953, Smith and Conley 1954) that pregnancy may precipitate acute exacerbations of the disease for the first time Our observations confirm this since in our series there were 3 previously asymptomatic primiparas (cases 5, 8, and 9) with sickle-cell anæmia, who had symptoms for the first time during pregnancy Case 4 only had symptoms in the course of earlier pregnancies There were 6 previously asymptomatic cases of sickle-cell/hæmoglobin-C disease and of them only 1 showed any symptoms and these were mild and postpartum The only case (number 11) with previous symptoms had a splenic infarct which occurred two weeks postpartum

With regard to reports suggesting that the maternal hazard may be greater in sickle-cell/hæmoglobin-C disease than in sickle-cell anæmia (Smith and Conley 1954, Edington 1957), our experience in Jamaica is conflicting No serious complications, either maternal or fœtal, were seen in any of our 7 cases of sickle-cell/hæmoglobin-C disease The reason for this discrepancy may be the accepted variation in the clinical course of this condition in the non-pregnant In many instances the abnormality may remain clinically undetected and may only be uncovered in the course of family studies A good example of this situation is case 17 who had normal and uneventful deliveries of her four children, and was only diagnosed during investigation of her eldest child who had sickle-cell anæmia We have up to the present seen 88 cases of sickle-cell/hæmoglobin-C disease and more than half of these have never had any significant symptoms

It is likely that pregnancy does not materially affect the natural history of sickle-cell/hæmoglobin-C disease It seems permissible therefore to suggest that previous reports dealing with fatal cases of sickle-cell/hæmoglobin-C disease or those with severe exacerbations are probably highly selected and do not take into account the asymptomatic cases which would have been diagnosed only if routine hæmoglobin electrophoresis had been performed The same may to a lesser degree be true for sickle-cell anæmia

Delivery and Fœtal Hazard

Spontaneous deliveries occurred in 14 instances, but cæsarean section was performed in 3 cases of sickle-cell anæmia In case 6 the decision to perform a cæsarean section was taken because of a grossly deformed and contracted pelvis, which was a result of her sickle-cell anæmia She had had an arthrodesis of her right hip six years previously for avascular necrosis of the head of the femur The association of this latter condition and sickle-cell disease is well known (Golding et al 1959) In case 7 the cæsarean section was performed because of fœtal distress, and the presence of sickle-cell anæmia did not influence the decision In case 8 there were repeated episodes of chest pain and dyspnœa at 38 weeks in an elderly primigravida with an unstable fœtal lie The decision to perform a cæsarean section was dictated by the clinical manifestations of sickle-cell anæmia

Histological examination of the placenta was performed in 10 instances and was unhelpful

The average birth-weight in the series (table I) is 5 lb 10 oz for the children of mothers with sickle-cell anæmia, and 6 lb 9 oz for those with mothers who have sickle-cell/hæmoglobin-C disease, as compared with an average figure for this hospital of 7 lb 4 oz This difference cannot be accounted for by prematurity, although the precise duration of the pregnancy was not always certain Hypertension in pregnancy is a recognised cause of low birth-weights in full-term infants, and it is likely that this low birth-weight is related to the diminished uteroplacental blood-flow known to occur in hypertension (McClure Browne and Veall 1953) A study of the uteroplacental blood-flow in sickle-cell disease would be valuable It may be permissible to postulate that erythrostasis of sickled red cells does occur in the uterine and decidual arterioles Alternatively the reduced birth-weight might be explained by the decreased amount of protein and other essential growth factors available to the fœtus as a result of the increased requirement for these substances in a mother with hæmolytic anæmia

It is stated that there is a high fœtal loss in sickle-cell disease The cause is not known, but it seems that there is an increased risk of intrauterine death or premature delivery in the event of a crisis The literature has been reviewed recently by Curtis (1959) In a series of 64 pregnancies in sickle-cell anæmia and sickle-cell/hæmoglobin-C disease he reported 52% surviving children in sickle-cell anæmia and 65 1% in sickle-cell/hæmoglobin-C disease These figures correspond closely to those previously reported In the present series (table I) there were no abortions and there was only one intrauterine death (case 3) associated with an episode of severe anæma in which the bone marrow was shown to be megaloblastic Treatment with folic acid produced a striking reticulocyte response and improvement of hæmoglobin level additional to that attributable to blood-transfusion

In previous pregnancies not observed in this hospital three abortions occurred out of 19 pregnancies in the whole series In addition one viable infant was lost in a multipara (case 1) in the course of her fourth pregnancy It occurred after a prolonged labour of 60 hours at home without medical care This patient gave no symptoms referable to sickle-cell anæmia until $2^{1}/_{2}$ years after the stillbirth She came from a large family described elsewhere (MacIver and Went 1958)

Management

Patients with sickle-cell disease in pregnancy should in general be treated conservatively They should be seen in the antenatal clinic more frequently than usual and should be carefully followed hæmatologically Patients with sickle-cell disease usually have adequate iron stores, and although there can be no harm in giving oral iron, parenteral iron therapy is contraindicated unless there is definite evidence of iron deficiency Careful attention should be paid to a good diet of adequate protein content. Patients should be admitted to hospital a few weeks before delivery or at the first sign of a crisis Considerable clinical evidence exists that infections may precipitate crises in sickle-cell disease, and antibiotics may therefore be indicated During a crisis the patient should be treated conservatively and confined to bed Treatment of sickle-cell disease with anticoagulants, corticotrophin, alkalis, and acetazolamide have all been advocated but do not seem to produce any significant effect.

Patterson and Sprague (1959) suggest that blood-transfusions in patients with sickle-cell anæmia are in general contraindicated, and our own experience confirms this. Should the hæmoglobin level fall below 6·0 g. per 100 ml., however, transfusion is required. The normal hæmoglobin level in sickle-cell anæmia is around 8·0 g. per 100 ml. (Went and MacIver 1958b) and in pregnancy the hæmoglobin level is not normally lower. If a patient with this level of hæmoglobin is transfused an inhibition of erythropoiesis results. In cases 5, 6, and 8 blood-transfusion resulted in a sharply diminished reticulocytosis and a temporary fall in bilirubin level. These returned to normal for sickle-cell anæmia as soon as the patient's hæmoglobin level had fallen to about 8·0 g. per 100 ml. Although there are undoubted advantages in a patient having a high hæmoglobin level at the time of delivery, Henderson (1950) reported 17 immediate reactions with 3 deaths in forty-four transfusions in sickle-cell anæmia.

Anæsthesia during delivery or cæsarean section does not in our experience present any special hazard provided oxygenation is adequate. Oxygen therapy per se is not required unless there is dyspnœa or evidence of fœtal distress. Unless indicated by other obstetrical complications there is no reason for premature induction of labour.

Inheritance and Incidence

Wherever possible the hæmoglobin genotypes of the parents and children of the patients with sickle-cell disease were determined. In the sickle-cell anæmia group all the parents and all the children studied carried a sickle-cell gene (table I). This is good supporting evidence that this group does not include any significant number of cases of sickle-cell thalassæmia. From our knowledge of the incidence of the sickle-cell trait in Jamaica (10·4%, Went 1957) one would expect approximately 1 in every 10 of these women to marry a man with the sickle-cell trait. This is confirmed by our results since a child of a woman with sickle-cell anæmia (case 6) also suffers from sickle-cell anæmia. The diagnosis in this case was made when the child was $2^1/_2$ months old. One patient with sickle-cell/hæmoglobin-C disease (case 17) also married a man with the sickle-cell trait and of the offspring 2 children have sickle-cell anæmia, 1 has sickle-cell/hæmoglobin-C disease, and 1 the hæmoglobin-C trait. It is of interest that in the series of children born of mothers with sickle-cell/hæmoglobin-C disease there is a striking preponderance of the C gene. Although the series is small we are convinced of its significance because we have regularly observed the same finding in other families. From a knowledge of the inheritance of S and C genes, which are alleles, this observation is difficult to explain, but it raises the possibility that in some way a C gene may have a better chance of resulting in a viable infant.

A comparison of the incidence of sickle-cell disease in pregnancy in our own series with published data on Negro patients in the United States shows a remarkable discrepancy. Anderson and Busby (1949) reported 11 cases from the Johns Hopkins Hospital over a 20-year period (an incidence of 1 in 1296 deliveries), Beacham and Beacham (1950) found 24 cases in New Orleans over 12 years (1 in 1666), while Adams et al. (1953) reported 13 cases in Memphis over 12 years (1 in 2075). In Jamaica at the University College Hospital 15 of the 17 cases reported here were studied between January, 1957, and December, 1959. During this period there were 4500 deliveries, which gives an incidence of 1 case of sickle-cell disease in 300. It is possible that even during this period of intensive study a few asymptomatic cases passed through the obstetric department undiagnosed. However this may be, the maximum calculated incidence† of sickle-cell anæmia and sickle-cell/hæmoglobin-C disease together in the general population reaches a figure of 1 in 235 which approaches our observed figure in this series. For the purpose of the calculation it is assumed that all affected children have reached adult life and are of normal fertility, an assumption which though not strictly justified, does not materially affect the calculation since either an increased mortality or decreased fertility would lower the calculated incidence figure, which would then be even nearer to the observed figure.

The coincidence of sickle-cell disease and pregnancy in this series is 4 to 6 times more frequent than in previous reports. In fact, sickle-cell disease seems to be as frequent amongst pregnant women in Jamaica as in the general population. This is in sharp contrast to the previously accepted concept that many women with sickle-cell disease were either infertile or incapacitated or died at an early age. The fact that very many patients with sickle-cell disease in Jamaica do survive to adult life has been noted by Went and MacIver (1958b), who found nearly half their cases to be over 15 years of age. This finding was not in keeping with the estimated survival-rate of 20% in the United States (Neel 1951), or of 1 to 14% in Africa (Vandepitte and Colaert 1955, Jacob 1957). It seems permissible to conclude that one of the factors responsible for the much higher incidence of the disease in pregnancy is this apparently greater chance of survival of Jamaicans with sickle-cell disease. However, the principal reason for the comparatively large number of cases in this series must have been the adoption of routine tests for sickling in all pregnant women with a hæmoglobin level below 10·0 g. per 100 ml. In all cases with positive sickling tests, further laboratory investigations were undertaken, and 3 of the cases were discovered in this way. 5 other cases were discovered in the course of an electrophoretic survey to determine the incidence of abnormal hæmoglobins. Diamond (1959) has recently reported a series of cases of sickle-cell/hæmoglobin-C disease in pregnancy seen in London. 3 of these were migrants from Jamaica.

It seems that sickle-cell disease may be almost as frequent among pregnant women as among the general population in Jamaica.

Summary

(1) 17 patients with sickle-cell disease were followed through pregnancy. 9 of them had sickle-cell anæmia, 7 had sickle-cell/hæmoglobin-C disease, and 1 had an unusual form of sickle-cell thalassæmia.

(2) The maternal and fœtal hazards are discussed, and seem to be considerably less serious than in most other reports. Complications were more frequent in the puerperium. 5 out of 7 cases of sickle-cell/hæmoglobin-C disease had no complications at any time.

(3) The birth-weight of the infants in this series was very much below average.

(4) The incidence of sickle-cell disease amongst

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† The calculated figures are derived from a study of the incidence of the S and C genes in 1018 pregnant women attending the antenatal clinic (Went 1957). Of these women 10·1% had the sickle-cell trait and 3·0% the hæmoglobin-C trait.

pregnant women in Jamaica seems to be very similar to the incidence in the general population

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Addendum

After this article had been completed, one patient (case 17), who has sickle-cell/hæmoglobin-C disease, came to hospital with her eldest child who has sickle-cell anæmia The child had a hæmoglobin level of only 2 0 g per 100 ml and was found to be in an aplastic crisis At this time the mother was 20 weeks' pregnant. 3 weeks later she returned with her third child who also has sickle-cell anæmia, again in an aplastic crisis (hæmoglobin 1 6 g per 100 ml) At this time the mother's hæmoglobin level was 10 2 g per 100 ml, but 2 weeks later she herself had to be admitted to hospital in an aplastic crisis (hæmoglobin 4 6 g per 100 ml) She also had pain in the back, wrists, and shoulders

She was given a blood-transfusion, after which she developed a splenic infarct and an attack of acute dyspnœa The radiological picture confirmed a clinical diagnosis of pulmonary infarction This patient was very ill, and in fact her crisis was as severe as anything we have seen in sickle-cell anæmia. Large numbers of nucleated red cells persisted in the peripheral blood for 2 weeks After she had been in hospital for 11 days she aborted, after which there was very rapid improvement of her clinical state 4 days after the abortion she had become apyrexial and her pulse-rate had returned to normal Thereafter her hæmoglobin level rapidly improved

The occurrence of 3 cases with an aplastic crisis in one family is of great interest and will be reported in detail elsewhere

PRIMARY BILIARY CIRRHOSIS

A CASE WITH SYSTEMIC LESIONS AND CIRCULATING ANTI-TISSUE ANTIBODY

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THE finding in 1957 of complement-fixing antibodies to human tissue antigens in the serum of a patient with primary biliary cirrhosis suggested that autoimmunity may play a role in the pathogenesis of this disease (Mackay 1958) The present investigations on a similar patient studied in our unit have provided additional evidence relevant to this hypothesis

Case-report

A 50-year-old housewife was first seen in the Royal Melbourne Hospital in March, 1959 3 years previously she had noticed persisting pruritus, pigmentation of the skin, and tiredness These symptoms had begun a few weeks after hysterectomy for uterine prolapse, prolonged ileus had complicated the postoperative period She had had severe lower back pain for 6 months 3 months before admission she had had a productive cough, and later pneumonia Additional symptoms included sore and " gritty " eyes, yellow scleræ, dark urine, and pale stools She had lost 10 kg in weight She had not had hepatotoxic drugs, and no case of infective hepatitis was known in her neighbourhood She had had syndactyly from birth

The skin showed brown pigmentation and slight jaundice, but no spider nævi or xanthomata There was firm, regular, non-tender enlargement of the liver to 4 cm below the right costal margin, the spleen was just palpable The urine contained a trace of albumin and the centrifuged deposit showed only epithelial cells

Investigations

The hæmoglobin was 9 7 g per 100 ml, and the white-cell count was normal The prothrombin index was 64% of normal The lupus-erythematosus-cell test and Wassermann reaction were negative. The gastric secretions contained no free hydrochloric acid. The range of values for serum constituents (per 100 ml) over a 30-day period were bilirubin, 1 7–2 8 mg, albumin, 3 1–3 4 g, globulins, 3 7–4 4 g, γ-globulin, 1 6–1 8 g, alkaline phosphatase, 57–74 King-Armstrong units, cholesterol, 368 mg, total lipids (fasting), 1540 mg, urea (blood), 69–75 mg, calcium, 9 6–10 mg, and phosphorus, 2 6–3 2 mg The cephalin-flocculation test varied from — to +++, being most often negative The range for the serum oxalacetic-glutamic-transaminase was 45–103 units A 6-day fat-balance estimation showed 78% absorption of dietary fat. A calcium balance and an intravenous calcium-infusion test were interpreted as indicating both osteomalacia and osteoporosis

The complement-fixing titre of the serum to human liver and kidney antigens (A C I F reaction of Gajdusek 1958) was consistently raised, ranging from 128 to 256 Circulating antibodies to thyroglobulin (titre 160) were demonstrated by the tanned-red-cell hæmagglutination reaction, although there was no clinical evidence of thyroid disease

X-ray Examinations

The lumbar spine showed bony rarefaction and vertebral collapse, no zones of decalcification were seen, although the right pubis was irregular in outline The gallbladder functioned normally and contained a single gallstone

Laparotomy

The extrahepatic biliary system was normal apart from a single gallstone in an otherwise normal gallbladder The operative cholangiogram showed the extrahepatic bile-ducts to be patent and undilated, and the intrahepatic ducts to be slightly finer than normal Cholecystectomy was performed, and biopsies were taken

Biopsy Studies

Fibrosis and infiltration with lymphocytes and plasma-cells in the portal tracts of the liver suggested an active chronic non-obstructive cholangitis (fig 1) The cellular infiltrations occasionally formed follicles and invaded the liver lobules Polymorphonuclear leucocytes were scanty The changes were those of an early primary biliary cirrhosis

Biopsy of the right kidney (figs 2 and 3) showed striking changes The cortex was densely infiltrated with lymphocytes and plasma-cells, there was considerable tubular destruction and some glomerular sclerosis

Suction biopsy of the stomach (fig 4) revealed severe chronic atrophic gastritis with loss of specialised cells and invasion of the mucosa with lymphoid aggregates

The gallbladder wall was histologically normal A cystic

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* Working with the aid of a grant from the National Health and Medical Research Council of Australia

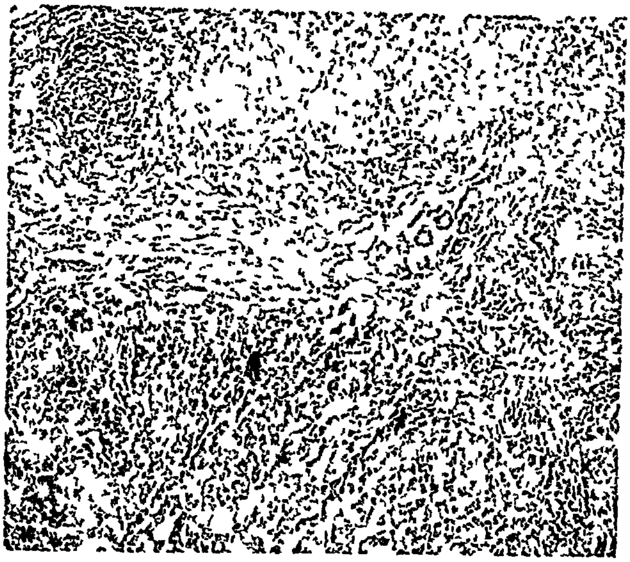

Fig 1—Liver biopsy specimen showing fibrosis and focal collections of lymphocytes and plasma-cells invading the liver lobules from the portal tracts The changes are those of an early biliary cirrhosis (Hæmatoxylin and eosin ×100)

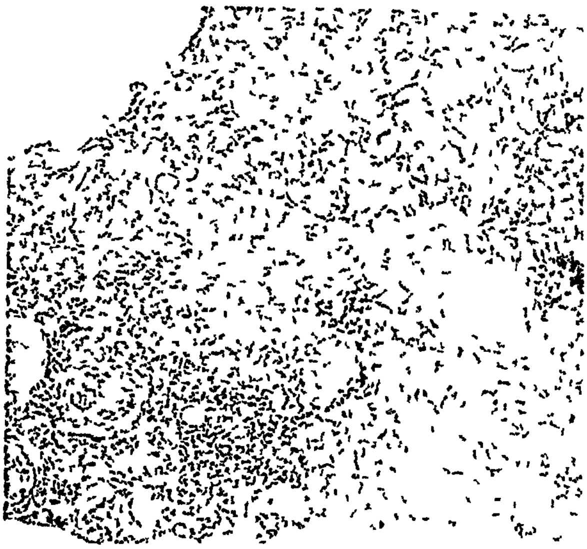

Fig 2—Kidney biopsy specimen The renal cortex shows disorganisation of architecture, glomerular and tubular destruction, and diffuse cellular infiltration: interstitial nephritis (H & E. ×100)

duct lymph-node showed follicular hyperplasia and sinus catarrh A skeletal muscle biopsy specimen from the abdominal wall was normal

Summary—A 50-year-old woman presented with pruritus, jaundice, and backache Biochemical tests indicated biliary obstruction and hyperlipidæmia Laparotomy showed no evidence of extrahepatic biliary obstruction Circulating antibodies to human tissue antigens were demonstrable Lymphoid-cell infiltrates were present in biopsy specimens from the liver, renal cortex, and gastric mucosa

Discussion

Many names have been coined for the idiopathic non-obstructive biliary cirrhosis of middle-aged women, including xanthomatous, intrahepatic, non-obstructive, cholangiolitic, and Hanot's biliary cirrhosis Primary biliary cirrhosis (Ahrens et al 1950), however, is the most widely accepted term

Primary biliary cirrhosis has been regarded essentially as a disease of the liver, the other manifestations such as xanthomatosis, portal hypertension, and bone-disease being secondary But the biopsy specimens from the liver, kidney, and stomach in the present case enable concepts of primary biliary cirrhosis to be taken a stage further These showed in common both destruction of tissue and dense aggregates of lymphocytes and plasma-cells, indicating that the process responsible for the cholangiolar lesion may involve other organs as well thus, primary biliary cirrhosis of the liver may in fact represent but one manifestation of what is potentially a multi-system disease

The circulating complement-fixing antibodies to human tissue antigens in primary biliary cirrhosis are in keeping with our previous findings Such antibodies are not regarded as having cytotoxic properties or organ specificity, but rather as indicating that immunological

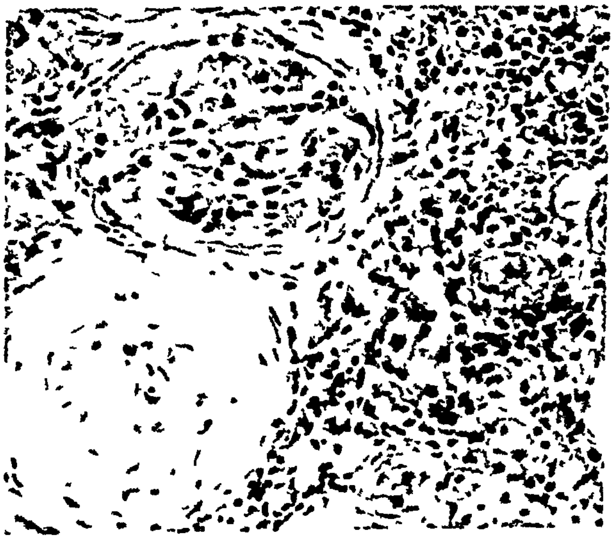

Fig 3—Kidney biopsy specimen One glomerulus shows capsular thickening and adhesions the other is sclerosed. There is tubular damage The cellular infiltrate comprises lymphocytes, plasma-cells, and histiocytes (H & E. ×400)

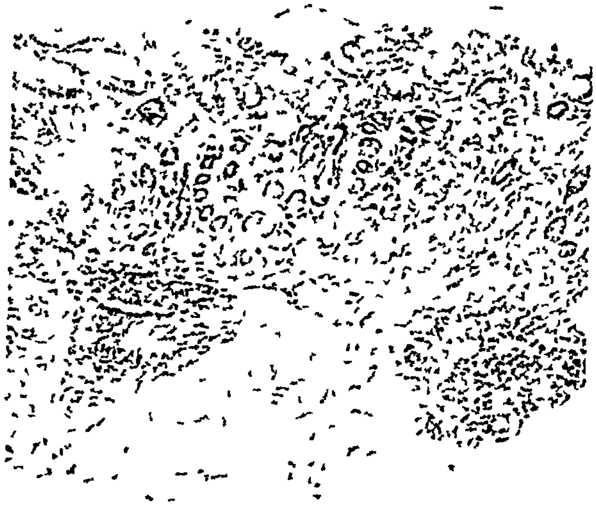

Fig 4—Gastric biopsy specimen, showing diffuse atrophic gastritis with focal collections of lymphoid cells in the deeper layers of the mucosa (H & E. ×100)

mechanisms are somewhere at fault. Significantly, the disease most consistently associated with such high titres of anti-tissue antibody is systemic lupus erythematosus (Mackay and Larkin 1958)

At present, it is surmised that non-circulating antibodies, or what Burnet (1959) terms "immunologically competent cells", are implicated in the pathogenesis of tissue-destroying immunopathies This type of immune reactivity also subserves delayed, tuberculin, or homograft immunity In autoimmune disease immunologically competent cells react damagingly with tissue components, liberating fresh antigen, this leads to further stimulation of immunologically competent cells to fresh damage, and thus to the establishment of a self-perpetuating disease process

How such diseases are initiated is uncertain In the case of thyroiditis, Roitt and Doniach (1958) favour an immune response to "unfamiliar" or normally "inaccessible" thyroid antigens which may be liberated after cell damage of any kind In terms of Burnet's clonal selection hypothesis (1959), somatic mutation among immunologically competent cells could, in the absence of the normal homœostatic control, lead to proliferation of "forbidden" clones of cells capable of reacting with host components previously tolerated The occurrence and emergence into activity of such mutations may be determined by constitution, the ageing process, endocrine imbalance, or other factors The anti-host reactions of lymphoid neoplasms, which Kaplan and Smithers (1959) have recently compared with "homologous disease" of experimental animals, may also be cited as examples of tissue damage attributable to "forbidden" clones

Thus there is evidence that primary biliary cirrhosis should be classified within the group of tissue-destroying immunopathies These are best exemplified at present by Hashimoto's thyroiditis, but they may also include Sjogren's disease, the lupoid type of chronic hepatitis, and related manifestations of visceral lupus erythematosus Some of these conditions often occur singly, but, as in the present case, there may be random patterns of systemic disease

Summary

As in a case previously reported from this unit, primary biliary cirrhosis in a 50-year-old woman was associated with an increased serum level of γ-globulin and elevated titres of complement-fixing antibodies to human liver and kidney antigens

Biopsy specimens from the liver, kidney, and stomach all revealed pronounced parenchymal damage and dense infiltrations of lymphoid cells

These serological, biochemical, and histological findings provide further evidence for the inclusion of primary biliary cirrhosis within the group of visceral immunopathies, which includes Hashimoto's disease, Sjögren's disease, lupoid hepatitis, and related manifestations of visceral lupus erythematosus

I am indebted to Dr Mary Ralston for assistance with histological interpretations, to Mr E. Matthaei for the photomicrographs, to Dr Roger Melick and Dr Sara Weiden for biochemical data, and to Miss Lois Larkin for performing serological tests

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MYOCARDIAL INFARCTION DURING PREGNANCY AND PUERPERIUM

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MUCH has been written about heart-disease complicating pregnancy, and it is known that between 1 5 and 3% of women attending antenatal clinics have some form of heart-disease This, however, is mostly rheumatic (Hamilton and Thomson 1941, Mendelson 1944, Stromme and Kuder 1946, Haig and Gilchrist 1949, Vander Veer and Kuo 1950, Fitzgerald et al. 1951) There is little mention of ischæmic heart-disease, and, as serious atheroma is uncommon in women of childbearing age, it is unusual to see clinical evidence of it at this time. Bramwell and Longson (1938) and Campbell (1947) said that they had never encountered it, and Jones (1951) reported only 1 case of true angina of effort among 1500 pregnant cardiac patients seen during fifteen years

Improved diagnosis and increased interest in atherosclerosis have led to a better understanding of its varied aspects, and many physicians have now reported women with known ischæmic heart-disease becoming pregnant (Horowitz et al 1943, Levine 1951, Mendelson 1952, Klein et al 1953, Oliver 1953, Lyons and Lyons 1954, Forssell and Brunila 1957) Such, however, are usually older women, and the atheroma is often associated with hypertensive heart-disease, diabetes mellitus, or familial hypercholesterolæmia Judging by the literature, myocardial infarction during pregnancy or in the immediate postpartum period is rare Spiegelberg's original case of a woman with angina who had a normal delivery and survived was published in 1871, and in 1952 Mendelson could find only 21 reported cases which appeared consistent with this diagnosis

Many of the earlier ones, of course, were unproved, occurring as they did before the days of electrocardiography or even before myocardial infarction was generally recognised as a clinical entity The first confirmed case during pregnancy was described by Katz in 1922, though six years before this Kolisko (1916) had reported a death from coronary thrombosis a month after delivery It was not until 1935 that the first case with electrocardiographic proof of infarction was reported by Reiss and Frankenthal, and occasional authentic cases have appeared since then to make a total of 26—23 during pregnancy or labour and 3 in the puerperium (see table I)

We have recently diagnosed myocardial infarction in association with pregnancy in two young women One, aged 22, had a major anterior infarct two weeks from term, and the other, aged only 17, had a posterior infarct six days after delivery Neither had severe anæmia, hypertension, diabetes mellitus, or other metabolic disorder

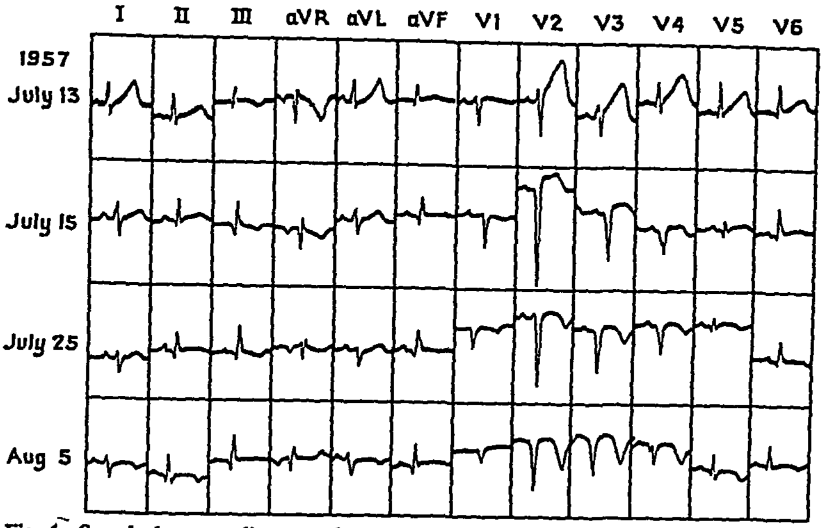

Fig 1.—Serial electrocardiograms in case 1, showing the pattern of recent anterior transmural myocardial infarction.

Cases

Case 1.—The patient, aged 22, was well until July 13, 1957, when she was in the 38th week of her second pregnancy. While shopping, she experienced sudden severe central retrosternal pain, which radiated to her left shoulder and down her left arm. When admitted to hospital, she was sweating and anxious and had vomited several times. There was no significant personal or family medical history.

The pain persisted intermittently for two days and serial electrocardiograms showed the pattern of recent anterior transmural myocardial infarction (fig. 1). The serum-cholesterol level was 265 mg. per 100 ml. She was treated with rest and sedation, and, to avoid the strain of labour, cæsarean section was carried out on July 26, two days before her estimated date of delivery. Her recovery was uneventful and the baby (6 lb. 11 oz.) was well. She remains well, and is normotensive, with no symptoms to suggest ischæmic heart-disease. She has in fact completed another pregnancy, this time without incident, delivering herself almost exactly two years after her cardiac infarct. Six months after this delivery her serum-cholesterol was 270 mg. per 100 ml. and her β-lipoproteins slightly elevated.

Case 2.—The second patient, a primigravida, was only 17 and rather unintelligent. She had had occasional choreiform movements of her upper limbs and head for about four years. These had become more severe during the second half of her pregnancy, and had caused her much anxiety. She went into labour three weeks before term, delivering herself spontaneously, on Dec. 28, 1958, of a baby weighing 4 lb. 10 oz. Soon afterwards she became emotionally upset and was seen by a psychiatrist, who took her under his care as a case of chorea gravidarum.

Although there was no history of acute rheumatism, an electrocardiogram was recorded on Jan. 8, 1959, when unexpectedly the pattern of a recent posterior myocardial infarction was found (fig. 2). On close questioning of the girl it transpired that she had complained of central chest pain three days after delivery, was pale and clammy at that time, and had vomited. She had attributed the whole episode to some plums eaten shortly before.

When transferred to a medical ward, she was dull and emotionally unstable, but there were no signs of chorea and the only evidence that she might have had active rheumatism was a serum-antistreptolysin titre of 300 units per ml. It was also noted that she had active acne vulgaris. Her serum-cholesterol concentration was 276 mg. per 100 ml., and the α/β lipoprotein ratio was 1/7.8. With rest in bed and sedation she made uneventful progress. When last seen some four months later she was symptom-free and appeared to be in good health, while the serum-cholesterol level had fallen to 153 mg. per 100 ml.

Discussion

Much is now known about blood-lipid patterns and how they can be influenced or altered by hormones or diets, but the role of fat metabolism in the ætiology of atherosclerosis remains uncertain. This lack of demonstrable cause-and-effect relation is well exemplified in pregnancy. During normal pregnancy the lipid pattern alters considerably: the total cholesterol increases and its distribution between the α and β lipoproteins alters to resemble that found in men with ischæmic heart-disease, more cholesterol being attached to the β lipoprotein (Oliver and Boyd 1955). Of the many substances that have been used therapeutically or experimentally to influence the plasma lipids, œstrogens are among the most effective in restoring the so-called non-atherosclerotic pattern (Eilert 1949, Barr 1953). Yet during pregnancy, when circulating œstrogens greatly increase, the effect seems to be exactly the opposite.

In spite of this change in lipid distribution, coronary disease in pregnancy is rare. Many complex hormonal and metabolic changes are taking place at this time, and we must suppose either that the pregnant woman's intima is in some way protected from her "atherogenic" lipid pattern or that these patterns are not in fact causally related to thrombosis or atherosclerosis. If the former is true, an occasional breakdown of the protective mechanism would explain the myocardial infarcts which occur at this time. These may be the result of thrombosis in otherwise healthy coronary arteries, as in the case described by Muir (1960).

Changes in the circulating lipids during pregnancy are gradual, increasing until about the 33rd week and then diminishing slowly during the later weeks and puerperium (Oliver and Boyd 1955, Watson 1957). It might be expected that most myocardial infarcts would take place in the 8th month when the lipid pattern is most abnormal. Yet in only 1 of the reported cases has it occurred at this time, the rest being widely scattered and almost equally divided between the first and second halves of pregnancy. A quarter have been before the end of the 2nd month (table II) at a time when the measurable alteration in lipid patterns is relatively small.

Few of the patients have been very young, most being

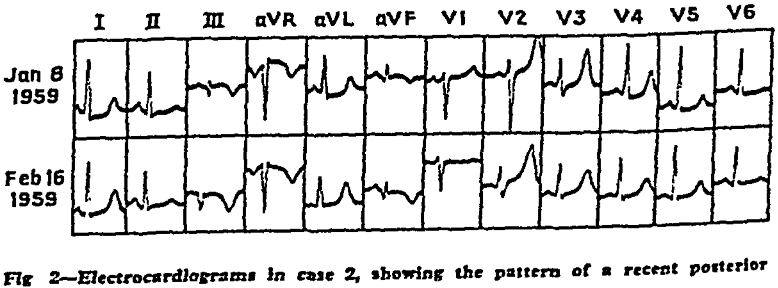

Fig 2.—Electrocardiograms in case 2, showing the pattern of a recent posterior myocardial infarction.

TABLE I—CASES OF MYOCARDIAL INFARCTION DURING PREGNANCY OR PUERPERIUM CONFIRMED BY ELECTROCARDIOGRAPHY OR NECROPSY

Author	Age	Blood-pressure	Stage of gestation	Parous	Fate	Remarks
Kolisko (1916)			1 month postpartum		Died	Thrombosis in branch of left coronary
Katz (1922)	33	?	Onset of labour	Yes	Died	Coronary atheroma and myocardial infarction
Reiss and Frankenthal (1935)	45	210/140	Onset of labour	Yes	Survived	Syphilitic
White et al (1935)	22	115/70	2nd month	No	Survived	
Jensen (1938)	39	132/86	5th month	Yes	Survived	Rheumatic heart-disease
Hamilton and Thomson (1941)	?	186/110	2nd month	Yes	Survived	
Goldberger and Pokress (1950)	37	?	4th month	Yes	Survived	Syphilitic. Rheumatic heart
Leff (1950)	27	130/80	6th month	No	Survived	
Mendelson (1952)	42	210/120	5th month	Yes	Survived	Anticoagulant therapy
Stewart (1952)	? 42	Hypertensive Hypertensive	8th month 19th week	Yes Yes	Died Survived	Acute pulmonary œdema Anticoagulant therapy
Brock et al (1953)	34	158/98	2nd month	Yes	Survived	Diabetic. Anticoagulant therapy
Antonius et al (1955)	36	144/98	7th month	Yes	Survived	
Gordon (1955)	? ? ?	? ? ?	? ? ?	? ? ?	Died Died Died	3 cases from death certificates 2 proved by necropsy, 1 by E.C.G
Siegler et al. (1956)	38	152/92	6th week	Yes	Survived	Diabetic, hypertensive. Angina 5 years Anticoagulant therapy
Levine and Lanning (1956)	37	Not hypertensive	At term	Yes	Survived	Anticoagulant therapy
Freedman and Gilbert (1956)	28	120/90	17th day postpartum	No	Survived	Anticoagulant therapy
Forssell and Brunila (1957)	38 44	185/110 190/130	1st month 4th month	No Yes	Survived Survived	Infarct during reserpine therapy Anticoagulant therapy
Myers and Sharpe (1957)	39	125/80	6th week	Yes	Survived	Anticoagulant therapy
Maternal Health Committee, Ohio State Med Assoc. (1958)	35	185/110	During labour	Yes	Died	Myocardial infarction and coronary atherosclerosis
Muir (1960)	26	?	5th month	?	Died	Large thrombus in a coronary artery, vessels appeared normal
This paper	22 17	130/78 120/70	38th week 3rd day postpartum	Yes No	Survived Survived	

TABLE II—STAGE IN PREGNANCY AT WHICH INFARCTION TOOK PLACE

Month	1	2	3	4	5	6	7	8	9	Term	Puerperium
Number of cases	1	5		2	4	1	1	1	1	4	3

36 years old or over, and many of them had arterial hypertension, though there is no correlation between either age or blood-pressure and the stage in gestation when infarction took place Of the 6 young patients, none of whom appeared to be hypertensive or diabetic, all but 1 had their infarction later in pregnancy—3 of them around term

It is interesting that most patients survived their infarcts and did remarkably well Only 8 died In 4 of these, the diagnoses were made retrospectively from a survey of death certificates or necropsy reports, in the other 4 death was sudden and no specific treatment was possible Of the 18 who survived, 8 of those recently reported have had anticoagulant therapy, without ill effects even when it was used immediately after delivery (Levine and Lanning 1956)

Our patients had no specific treatment for their infarcts and both did well The first had a cæsarean section at term to spare her recently infarcted ventricle from strain during labour The full precautions taken against sudden cardiac emergencies were fortunately not required, and the operation and postoperative course were uneventful We think this is the correct method of delivery in such cases, and it is significant that 2 of the 4 sudden deaths which have been reported were during labour

Summary

Myocardial infarction during pregnancy or the puerperium appears to be rare In the two cases recorded here the patients' ages were 22 and 17 In one of them the condition was diagnosed only through a fortuitous electrocardiographic recording, and it may well be that cases of this type often pass unrecognised

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LOCAN PESSARIES IN THE TREATMENT OF TRICHOMONAL VAGINITIS

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We report here three small clinical trials of 'Locan' pessaries for the treatment of trichomonal vaginitis These trials were carried out in the clinics for venereal disease at St Thomas' Hospital, the London Hospital, and Oldchurch Hospital The results are compared with those of a control series which was treated with acetarsol pessaries

Locan pessaries each contain amethocaine gr $^1/_6$, amylocaine gr $^1/_{12}$, solution of benzalkonium chloride $^1/_3$ minim, lactic acid gr $^1/_2$, and lactose gr 4 in a non-staining oil-free base Amethocaine and amylocaine have been shown to possess trichomonacidal activity in addition to their local anæsthetic action Benzalkonium chloride is also trichomonacidal

Stewart et al (1957) found that each of 68 attacks of trichomonal vaginitis was controlled by four weeks' treatment with locan pessaries and that only 2 (3%) were not controlled by two weeks' treatment Using acetarsol for two weeks, 25 of 79 attacks (32%) were not controlled The recurrence-rate was almost equally common after treatment of attacks with acetarsol and with locan—namely, 26% and 28% respectively

Method

Patients in the first series were treated with one pessary night and morning for six days Patients in the second series received one pessary nightly for fourteen days After Stewart et al. (1957) had suggested that the optimum treatment was one pessary night and morning for two weeks, a third series of patients were treated by that method The control series was treated with acetarsol one pessary night and morning for two weeks

Trichomonas vaginalis was demonstrated microscopically in a wet smear of the vaginal discharge in all cases before treatment was started, and progress was assessed by examination of further wet smears If trichomonads could not be demonstrated immediately after treatment was completed the infestation was considered to have been controlled, those cases in which trichomonads were still present were classed as immediate failures, and treated by other methods (No patient was given a second course of locan, in view of the known propensity of local anæsthetics to give rise to sensitivity reactions) Those cases in which trichomonads recurred in the vagina within three months of the end of treatment were classed as late failures (No attempt was made in these cases to discriminate between relapse and reinfestation as it was found impossible to obtain accurate information on this subject)

TABLE I—RESULTS OF TREATMENT WITH LOCAN AND ACETARSOL

Treatment	No of patients	Immediate control	Failures		
			Immediate	Late	Total
Locan					
1 b d for 6 days	19	15	4 (*21%*)	14 (*73%*)	18 (*95%*)
1 nightly for 14 days	8	4	4 (*50%*)	1	5 (*62 5%*)
1 b d for 14 days	36	32	4 (*11%*)	12 (*33%*)	16 (*44%*)
Total	63	51	12 (*19%*)	27 (*43%*)	39 (*62%*)
Acetarsol 1 b d for 14 days	60	54	6 (*10%*)	22 (*37%*)	28 (*46%*)

TABLE II—DEFAULTERS AND NUMBER OF PATIENTS IN EACH TRIAL

Treatment	Total no of patients	Defaulters		Treatment stopped because of sensitivity
		Initial	Late (2–6 weeks)	
Locan	81	18	11	5
Acetarsol	82	22	12	0

Results

The results after subtraction of initial defaulters (i e, those who defaulted before treatment was finished) are shown in table I

The number of defaulters and the total number of patients in each trial are shown in table II It will be seen that the figures are closely similar

Sensitivity Reactions

In 5 of the patients using locan, treatment had to be stopped because of untoward reactions In 4 these took the form of vulval "burning" and irritation following insertion of the pessary, and in 1 there was gross vulval œdema and a generalised urticarial rash 1 of these patients gave a history of a previous course of treatment with locan, and another of a previous reaction to cocaine lubricating ointment None of the patients using acetarsol developed any untoward reaction

Conclusion

Increasing the dosage and prolonging the period of treatment with locan pessaries led to improved therapeutic results One pessary of locan inserted night and morning for two weeks gave results comparable with those obtained with a similar dosage of acetarsol Locan therefore was no more effective than acetarsol and, because sensitivity reactions occurred in 5 out of 63 patients followed in our series, these pessaries should be used with caution

Summary

63 patients were followed after the treatment of trichomonal vaginitis with 'Locan' pessaries The results were compared with those in a similar series of 60 patients treated with acetarsol pessaries

Locan pessaries administered twice daily for fourteen days resulted in failure in 44% of cases, compared with 46% for acetarsol Shorter or less intensive treatment with locan resulted in a higher failure rate

Sensitivity reactions occurred in 5 out of 63 patients

The evidence suggests that locan is no more effective than acetarsol, and it may cause sensitivity reactions It should therefore be used with caution if at all

We should like to thank Dr C S Nicol for permission to publish details of cases under his care at St Thomas Hospital, and Allied Laboratories for the supply of 'Locan' pessaries

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Preliminary Communication

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

RESEARCH has been hampered by the lack of a suitable technique for producing thrombosis in laboratory animals A significant advance was, however, reported last year by the American workers Thomas and Hartroft,[1] who had produced myocardial infarction in the rat by dietary means Applying their technique we have obtained useful information on the development of atherosclerosis and thrombosis In the rat, we have been able to produce lesions resembling those of atherosclerosis and furthermore to produce thrombosis without atherosclerosis The experimental details are given elsewhere [2 3]

Rats were fed two main diets One contained 40% butter, 0 3% thiouracil, 5% cholesterol, and 2% cholic acid, while in the other the butter was replaced by 40% arachis oil Butter contains more saturated fatty acids and less linoleic acid than arachis oil Both groups of animals survived about a hundred days Those fed butter died with obstructive thrombosis of the cardiac chambers, aorta, coronary arteries, and renal veins, lesions resembling atherosclerosis were not found Those fed arachis oil developed fibroelastic thickenings of the proximal aortic and coronary-arterial intima with some lipid infiltration of the base of the lesion, thrombosis was not seen These experiments thus reinforce the view that atherosclerosis and thrombosis are not necessarily related phenomena, and that coronary thrombosis can occur in the absence of atherosclerotic plaques

Studies were also made of the cholesterol metabolism In both groups plasma-cholesterol was above the normal level but it was much higher in the group given butter We concluded, therefore, that plasma-cholesterol is not necessarily an index of atherosclerosis In contrast, the cholesterol content of liver and spleen, which was also raised in both groups, was higher in the group given arachis oil Essential fatty acids may therefore facilitate the deposition of cholesterol in the tissues and atherosclerotic plaques Though at variance with the view of Sinclair,[4] who believes that atherosclerosis is caused by a relative deficiency of essential fatty acid, our results are in agreement with those of Bottcher et al [5] The latter have shown that with increasing severity of atherosclerosis the linoleic-acid content of human plaques rises Our results certainly support the view that it is undesirable to feed saturated fats to patients with coronary thrombosis It is debatable whether essential fatty acids are a suitable replacement, since they may facilitate the deposition of cholesterol in atherosclerotic plaques

Current work is directed towards establishing which glycerides in butter and arachis oil are responsible for the different lesions observed in our experiments To this end, we are feeding the above-mentioned diet in which butter is replaced by different animal or vegetable fats or synthetic glycerides

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New Inventions

A PORTABLE ARTIFICIAL KIDNEY

AT last there has been an awakening of interest in artificial kidneys

Many patients who would benefit from their use are denied the opportunity One reason is the lack of artificial kidneys Secondly, the existing models are complex and powerful, requiring an expert surgical team to connect them to the patient in order to obtain the high flow-rates used, and needing even more skilled biochemical and medical supervision to cope with the rapid changes in body electrolytes Thirdly, renal dialysis is only one aspect of the treatment of renal or hepatic failure and many poisonings, and, fourthly, the ill or injured patient cannot always be transported to a specialist renal unit.

To get over these difficulties we need an artificial kidney which is simple, effective, safe, robust, and portable It should be capable of variable clearances, which should be easily controlled and monitored It should also be capable of a high degree of ultrafiltration, so as to dehydrate and to facilitate rapid electrolyte exchanges Hæmolysis should be negligible and the priming volume of the extracorporeal circuit should be so small that stored blood need not be used Leakage, if any, should be from the patient to the machine, to avoid the risk of flooding his circulation with unsterile dialysing fluid If possible, the unit should incorporate the pumping channels needed for regional heparinisation and for administering vasopressors Sterilisation should be simple Bearing in mind all these requirements, this unit was designed.

THE UNIT

The artificial kidney here described has two main components—a dialyser, which can be used for ultrafiltration, and a multi-channel metering pump

Dialyser (fig 1)

The dialyser, which may be used by itself, consists of three 'Perspex' plates, each 14 in square and 1 in thick. The centre plate has a spiral groove engraved upon its upper and lower flat surfaces From the outside of the plate a smooth perspex connector leads into the beginning of the groove on the lower surface of the plate This groove is 0 5 cm wide and 2 mm deep and passes spirally to the centre of the plate, covering a distance of 50 ft It is then led through the centre of the plate into a similar groove on the upper surface, which it traverses for another 50 ft. to the periphery of the unit, where it is again connected to the surface of the plate with a smooth perspex connector The other two plates are grooved on only one surface the lower plate has a spiral on its upper surface which is a mirror image of that on the bottom of the centre plate, while the upper plate has a groove on its lower surface which is a mirror image of that on the top of the centre plate

These three plates are clamped together, with sheets of ordinary 'Cellophane' (British Cellophane 300 film commercial grade, which cost about a farthing per sheet) between them, thus converting the grooves into three channels One channel, for the patient's blood, is on the two highly polished surfaces of the centre plate, and is approximately 100 ft. long The second channel is between the cellophane and the bottom plate, separated from the patient's blood only by the cellophane, and is 50 ft long This is for dialysing fluid, which (on the opposite side of the cellophane) follows the blood round the spiral from the periphery to the centre, where it is led away to a drain The third channel is on the lower surface of the upper plate and follows the course of the last 50 ft of the blood channel this is for the second lot of dialysing fluid, which is again discarded

Thus the dialyser has 100 ft. of surface 5 mm wide, through

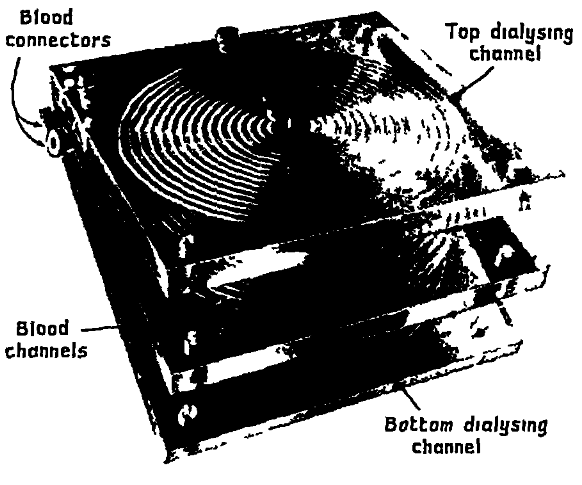

Fig 1—The dialyser. An "exploded" view showing the three perspex plates with the grooves for blood and dialysing fluid.

which exchange can take place. Efficiency of dialysis is doubled by changing the dialysing fluid halfway through the process, so that the blood is dialysed twice against a urea-free fluid. It is further increased by assembling the unit with the cellophane dry; for, when the machine is charged, the cellophane becomes corrugated as it expands, thus increasing the surface area, causing satisfactory mixing of the blood, and preventing streamline. Since the membrane is tough, the pressure differential between blood and dialysing fluid can be raised to well over 1000 mm. Hg, making the unit into quite an efficient ultrafiltrator.

This dialyser may be connected as an arteriovenous fistula, using arterial pressure to push the blood round and using gravity to force the dialysing fluid through the corresponding spiral grooves.

Pump

The whole unit is much more controllable when used with the pump. This is not an adaptation of a commercial pump but was designed, in conjunction with Medtec Laboratories, specifically for the kidney.

It is a multi-channel metering pump with laminæ massaging silicone rubber or 'Tygon' tubes. The pumping tubes are short, to reduce hæmolysis. The laminæ move in a parallel manner and the pumping head can be made of any width to accommodate as many channels as are required. The speed of the whole pump is variable, and the stroke volume of each tube can be varied between coarse limits by the choice of size of tube. The stroke volume of each tube can further be finely adjusted with occluders on the inlet side of the pump. Thus one pumping head will pump blood, dialysing fluid, heparin solution, heparin-reversing solution, radioisotopes for monitoring purposes, and other substances (such as vasopressors) which may be needed, leaving enough spare pumping channels to operate a second kidney if necessary. The range of outputs is between 250 ml. per min. and 0·1 ml. per min.

To maintain the pressure gradient across the membrane from blood to dialysing fluid, the pumping tube used for blood is of larger bore than the tube for the two dialysing pumps. As flow-rates increase, the greater length of the blood channel increases this pressure differential. Thus to increase ultrafiltration all that is necessary is to increase the blood-flow or decrease the flow of dialysing fluid. Further ultrafiltration may be obtained by doing both these things and constricting the blood outlet. If safe pressures are exceeded, the membrane will bulge into the dialysing fluid grooves and the flow of dialysing fluid will cease. This usually happens at a pressure differential of over 1200 mm. Hg. A leak would show instantly, for blood would pass into the clear dialysing fluid, which would be seen through the transparent dialyser and tubing.

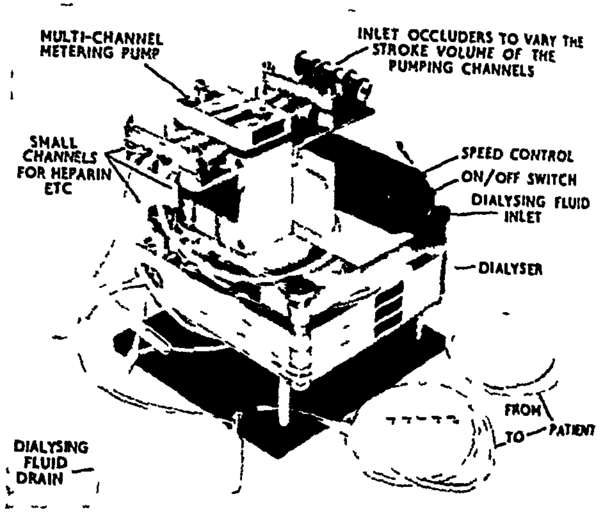
MULTI-CHANNEL METERING PUMP
INLET OCCLUDERS TO VARY THE STROKE VOLUME OF THE PUMPING CHANNELS
SMALL CHANNELS FOR HEPARIN ETC
SPEED CONTROL
ON/OFF SWITCH
DIALYSING FLUID INLET
DIALYSER
FROM
TO
PATIENT
DIALYSING FLUID DRAIN

Fig 2—The prototype kidney assembled ready for use.

The pump has two subsidiary heparin channels and a separate radioisotope monitoring channel, in addition to the main blood and dialysing fluid tubes. On the left of the dialyser are the two glass combined bubble traps and wells for the scintillation counters which may be used for monitoring purposes. A second neater and simplified unit is under construction.

Regional heparinisation is facilitated by the small output channels of the pump. Heparin (without preservative) may be pumped into the tip of the cannula used to withdraw blood from the patient. 'Polybrene' may be pumped into the tube leading back to the patient, far enough from the replacing cannula to allow mixing to take place and heparin neutralisation to begin. Protamine is unsuitable in the large quantities required.

A further small output channel may be used to meter radioactive bromine into the input side of the "kidney" so as to monitor the machine without the need for numerous biochemical studies. This is done by using a pair of scintillation or Geiger counters—one placed on the input side of the dialyser, and the other on the output side—to give an accurate measure of clearance of halogens to which all other substances may be related easily.

EXPERIMENTAL TRIALS

A dog was given a general anæsthetic and allowed to settle down for about half an hour. Using a Seldinger wire technique, or if necessary a cut-down, two cannulæ were inserted into the femoral veins so that the tips lay one in the common iliac vein and the other about 6 in. up the inferior vena cava. While this was being done the renal arteries were ligated through a laparotomy and urea was administered, to give the dog a blood-urea of around 500 mg. per 100 ml. Saline was dripped through the cannulæ very slowly for an hour before heparinisation in order to allow clotting in the laparotomy wound and in the groin wounds, before the administration of heparin. The "kidney" was then connected to the cannulæ, with the output side of the "kidney" connected to the cannula in the inferior vena cava. As the pump was started, heparin (2 mg. per kg. body-weight) was administered from the "kidney", which had been previously primed with saline and heparin. The radioisotope monitoring was started.

Using a flow-rate of 60 ml. per min. the unit cleared nearly 5 grammes of urea per hour. The consumption of dialysing fluid to give this clearance was about 110 ml. per min. These flow-rates were kept low so as to give some idea of what could be done to the blood-urea of correspondingly larger animals—such as man. The "kidney" is in fact capable of coping with flow-rates of up to 200 ml. per min. with a dialysing-fluid consumption of 380 ml. per min. If ultrafiltration is required, the consumption of dialysing fluid can be reduced.

To simplify the procedure, dialysing fluid was made up in packet form and merely tipped into 10-litre containers, which were then filled up to the 10-litre mark with warm tap-water Universal indicator was added and lactic acid poured in until the pH of the dialysing fluid was approximately 7 4 The dialysing fluid was discarded after it had been through the unit once. 'Carbogen' was not bubbled through the dialysing fluid, the temperature of which was kept at 40°C using a small aquarium-heater and thermostat. A dog which had a rather hæmorrhagic laparotomy survived seven hours' dialysis before it died. Dogs are notoriously delicate as experimental animals, and the fact that a dog can survive as long as this suggests that the unit could be run indefinitely in a human

The figures for blood-urea (mg per 100 ml) were

Initial blood-urea	350	After two hours	244
After one hour	310	After three hours	216

They correspond exactly to the predicted clearances obtained from the radiobromine.

An average halogen clearance through the machine—checked by using the radioisotope—is 70–80%, with flow-rates between 60 and 200 ml. per min Above these flow-rates the clearance starts to fall At a rate of 100 ml. per min the time taken for blood to flow through the dialyser is nearly four minutes This is quite long enough for efficient exchange to take place

COMMENT

It will be seen from these results that this artificial kidney does not approach the power of existing units, and some may therefore think it not powerful enough. Many, however, now see the need for a simple unit which can be left on for long periods for prophylactic dialysis, and for all forms of renal failure except that resulting from multiple injuries[1] (Even this last could well be treated with an original dialysis on the big kidney and maintenance on this unit) Use of this new model could greatly increase the number of patients treated, and it is capable of further development. Its portability should prove a very real advantage

I wish to thank Mr T Holmes Sellors and Mr J R. Belcher for their help in obtaining facilities for this work. I should also like to thank Dr J W Stewart and Dr R. Ekins for their help with the hæmatological and radioisotope monitoring

The machine was hand made under the supervision of Mr W G Spooner, of Medtec Laboratories, who spent many hours modifying its various components to achieve the finely engineered prototype.

ADDENDUM A CLINICAL TRIAL

Since this paper was written a successful 24-hour dialysis has been done on a patient for Sir Eric Riches The "kidney" was connected percutaneously and 200 g of urea was removed.

I should like to thank Mr Vernon Marshall, of Melbourne, whose experienced help was invaluable

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Reviews of Books

Mental Subnormality

W ALAN HEATON-WARD, M.B, D P.M., medical superintendent, Stoke Park Hospital Group Bristol John Wright. 1960 Pp 64 6s

MENTAL subnormality is used here to cover the two new terms "severe subnormality" and "subnormality" recommended by the Royal Commission and accepted in the Mental Health Act of 1959 Though new, these terms of course refer to an old subject, better known as mental deficiency in its various degrees Whether these new terms will really help our understanding of the subject is a moot point especially as the two are defined one on social and one on medical grounds But they are now legal terms and must be grasped, although they will not replace in clinical work the existing terms and systems of classification which recent research has made clearer

In any case, Dr Heaton-Ward deserves congratulation for producing this small book as an introduction to the subject general practitioners and students should find it very readable, and useful as a reference. He writes clearly and succinctly, and his facts are sound and well presented. The book will also serve social workers dealing with parents of defective children, in the advice it gives on the children's problems and attitude. It could indeed go further here, and give more advice on this very difficult subject, even if it curtailed the description of various rare types of mental defect. As the author realises, though there is a trend towards getting patients out of hospital, progress is bound to be very slow, and one stumbling-block is the attitude of society as a whole. This may well change if parents can learn to accept their own defective children with less guilt—and so less of its consequences—and to do this they need the concerted help and sympathy of all professional people involved.

Principles of General Physiology

5th ed Vol II L E BAYLISS, PH.D, department of physiology, University College, London London Longmans, Green. 1960 Pp 848 85s

FORTY-SIX years have passed between the appearance of the first edition of *Principles of General Physiology* by W M. Bayliss, and this second volume of the fifth edition written by his son. In the years between, biological science has changed as much as the aeroplane, in the one, man now bursts through the sound barrier, and in the other he is beginning to discover something about the nature of the chemical carriers of inheritance. Inevitably this volume has had to be almost wholly rewritten, but the author has inherited, and perhaps acquired also, something of his father's outlook, so that those who knew the first edition can feel a sense of continuity

Dr Bayliss is to be congratulated on a considerable achievement, it is unusual nowadays for two such volumes, covering an immense territory, to be written by one man. The new volume has retained some of the old chapter headings and again gives a limited number of useful leading references at the end of each chapter The subjects covered begin with the cell and nutrition, and pass to excitation and inhibition, effector and receptor organs, integrating systems, transport of metabolites and circulation of the blood, cell division, and homœostasis and control systems In each section a variety of examples from all parts of the animal and vegetable kingdoms are considered. Many readers will particularly admire the presentation in the sections on secretion and osmotic regulation, and the chapters on control and integrating systems are especially well written It is perhaps in these last two systems that some of the greatest changes in thought have taken place. But in all branches of biology techniques have developed tremendously in delicacy and accuracy, so that, apart from alterations in certain of our physiological concepts, there is an immense amount of new and important detail, especially relative to nerve and muscle. The new volume has retained many old figures, and this is not mere sentiment the figures are good and show how much accurate information the older workers obtained despite simpler and cruder methods—which should keep us humble. This volume is much easier reading than the first, and anyone with reasonable biological knowledge can enjoy it and painlessly learn a great deal. Clinicians will be helped to see how man fits into the general biological pattern One of the fascinations of a book such as this is its description of how the same physiological mechanism has been put to use in very different circumstances, and again, what extraordinary variations sometimes develop—for instance, in mollusca which make part of the digestive secretion in solid rod-like form and wear off portions of the rod by rotation against a chitinous plate This will certainly be an admirable book of reference, but it can also be picked up casually for a moment's pleasure.

Achievement

Some Contributions of Animal Experiment to the Conquest of Disease GEOFFREY LAPAGE, M.D , M SC , late lecturer in animal pathology, University of Cambridge Cambridge Heffer 1960 Pp 255 18s

TRADITIONALLY, little effort is made to contradict—far less to convert—those who oppose the use of animals in experiments To this end Stephen Paget wrote *Experiments on Animals* sixty years ago, but the book has not been reprinted since 1906 so it must be quite a rarity Now we have another book on the same lines by Dr Geoffrey Lapage, the distinguished parasitologist. It is a lucid and readable review of experimental medicine, especially in this country, and it begins about the place where Paget left off An especially valuable chapter—since it answers one of the commonest criticisms—is one on man as an experimental animal The author makes the necessary admissions without quibbling Experiments on animals cannot tell us all that we should like to know about disease in man, and sometimes they have been misleading Vivisection is not always painless (which may be quoted in the abolitionist journals), but almost unanimously we do our best to hurt any animal as little as possible (which may not be)

In an appendix the author gives a fair account of the system of licensing and inspection to which all vivisection is subject in Great Britain The most gratifying thing about this book is the width of interest and appreciation of fields other than his own which Dr Lapage displays Apart from his purpose in refuting the misinformed he has given an excellent account of important work in almost every branch of medicine It will interest many laymen far more than most of the books devoted to the " wonders " of medical science Will it influence the opponents of vivisection ? When heart so often beats head, we doubt it

The Massachusetts General Hospital 1935-1955

NATHANIEL W FAXON, M D , director emeritus, Massachusetts General Hospital, Massachusetts Eye and Ear Infirmary Cambridge, Mass Harvard University Press London Oxford University Press 1960 Pp 490 80s

NOW that a large part of the West End of Boston has been laid waste—a great slum clearance that will give Massachusetts General Hospital room for its imminent expansion—the time is ripe for another in the series of volumes of the history of that celebrated hospital, which was founded in 1811 as the third civilian general hospital in America, was the site of the first public demonstration of ether anæsthesia, and is one of the chief teaching hospitals for Harvard Medical School The last volume (by Dr F A Washburn) brought the story up to 1935, and the next twenty years have been chronicled by Dr Faxon, who was director of the hospital from 1935 to 1949 A year-by-year account of events is followed by a series of surveys of developments in research, teaching, and the work of various services, departments, and affiliated hospitals, and there is an appendix full of names and statistics The inevitable repetition is unimportant in a book that most people will use for reference But some chapters are fascinating, such as that about the " rise and fall " (rather the diffusion and concentration of his duties) of the hospital apothecary, who has absorbed various functions as they were presented to him—clinical medicine, medical records, photography, radiography—then as they became indigestible regurgitated them (except for the famous Walter J Dodd, who abandoned pharmacy in 1908 to become the full-time skiagrapher, and later died as the result of X-ray burns)

Readers may be surprised to learn that 1000 persons are taught there daily, for, besides undergraduate and postgraduate medical and nursing education, the hospital instructs many professions, from medical illustration to pastoral care Most outsiders will be surprised to know how many modern methods of diagnosis and treatment have been pioneered, if not originated, there the use of radio-iodine, cervical smears, nailing for femoral-neck fractures, cup arthroplasty, sympathectomy for hypertension, pericardectomy, megavoltage radiotherapy, deleading, and parathyroidectomy are some of them Outsiders will be interested in the reactions of the hospital to changes in the tenor of medicine and to outside events, such as the Cocoanut Grove fire of 1942 and the poliomyelitis epidemic of 1955, from both of which many valuable lessons were learned During the years covered by this book a blood-bank was set up, the metric system was adopted, the hypodermic tablet was abandoned, and the annual antibiotic bill rose from zero to $166,000, a third of the drug bill The startling change in social conditions since 1934 is brought home by one fact there was then so much unemployment among special-duty nurses that the maximum working day was cut to eight hours to spread the work

Manual of Skin Diseases

GORDON C SAUER, M D , assistant clinical professor of medicine (dermatology), University of Kansas School of Medicine London Pitman Medical Publishing Co 1960 Pp 269 70s

MOST doctors who enter general practice do so with an extremely meagre knowledge of skin diseases This is partly the fault of the medical curriculum, which allows very little time for the student to gain even a slight knowledge of dermatology, but it is also due to a paucity of textbooks which offer reliable and brief information

Professor Sauer has set out to correct this deficiency, and he has produced a readable and entertaining book which many may find difficult to put aside once they have started turning its pages The busy practitioner will be relieved to note the omission of lengthy discussions on ætiology, and references have been included sparingly One unusual feature is a chapter on the geographical distribution of skin diseases in North America, and we hope that future editions may include similar data concerning other continents There is a novel dictionary index which gives not only the page reference of diseases described in the text but a brief description of many less common conditions which would otherwise be omitted The information in some chapters is conveyed by dialogue, which is likely to leave a more lasting impression than if it were presented as a list of facts We feel confident that this book is a useful addition to the textbooks on elementary dermatology

Recent Advances in Clinical Pathology (*Series III* London J & A Churchill 1960 Pp 425 50s)—The ten years' wait for a revision of this book, under the general editorship of Dr S C Dyke, is amply compensated for by the results The contents are entirely new, and, as those of the previous volumes are by no means out of date, this has been designated " third series " and not " third edition " As before, there are four almost equal parts under section editors some idea of the scope and quality of treatment of the subjects can be gauged from the names—Mary Barber (antibiotic-resistant staphylococci), Payne (laboratory investigations in " failure to thrive "), Lehmann (hæmoglobinopathies), and Barr (cytological tests of chromosome sex), and there are many other good things One minor source of disagreement is that an equal number of pages in each section does not accurately reflect progress in a decade when some disciplines expanded more rapidly than others, and some readers may regret that there is nothing about recent progress in red-cell enzyme studies, alkaline-phosphatase stains in leukæmia, or sterilisation techniques in hospitals

Part of the value of such a book is its ability to keep both general and specialist pathologists informed of advances on as many fronts as possible, and the general editor is to be congratulated on his success

The Pædiatric Prescriber (Oxford Blackwell Scientific Publications 1960 Pp 214 15s)—Those who have to treat children will welcome this book by Dr Pincus Catzel It is handy for the pocket and full of information which is neither easily remembered nor often readily accessible Errors and omissions are few and there are useful blank pages for personal favourites A bargain at the price

THE LANCET

LONDON 3 SEPTEMBER 1960

Poliomyelitis: Attenuated or Inactivated Vaccine?

SINCE we last considered this topic[1] three important meetings have been held The first, in Moscow, and the second, in Washington, were concerned with attenuated vaccine The third was in Copenhagen—the Fifth International Poliomyelitis Congress, where progress with both varieties of vaccine was reviewed[2]

We suggested earlier that neither the safety nor the efficacy of attenuated poliovaccines had been demonstrated beyond question[1] Unfortunately, subsequent reports have not been entirely reassuring on safety, at least as regards some of the attenuated strains First, KIRCHSTEIN et al[3] have reported that the Cox and Koprowski type-1 strains cause paralysis in monkeys following intramuscular inoculation of large doses, the Sabin type-1 strain produces localised lesions but not paralysis Secondly, cases of paralysis have occurred both in Florida and in West Berlin in circumstances which suggest that Cox's strains or early human passages from them may have been the cause, but these two incidents are still being studied, and it is not proven that the vaccine virus rather than a wild virulent virus was responsible The unravelling of such incidents is exceedingly difficult If the causal virus differs notably in genetic markers it is almost certainly not derived from the vaccine virus As SABIN said at the Copenhagen meeting, the most serious incriminating evidence would be epidemiological—the concentration of cases in time and place in relation to a particular batch of vaccine—and indeed this is what has given rise to the present suspicions The isolated case due to increased individual susceptibility would escape recognition Such hypothetical cases are not considered important by the advocates of attenuated vaccine SABIN, in his impressive study in Toluca, Mexico,[4] noted that in this population of about 100,000 the natural immunisation of 90–100% of the children took four years and cost about 60 cases of paralysis Clearly in such a community a vaccine that achieved the same immunisation even at a cost of 1 or 2 cases would be well worth while—in fact SABIN achieved nearly as much immunisation in four months by vaccination, with no cost in paralysis, as occurs naturally in four years It should be noted, however, that in Mexico susceptibles over the age of 4 years are exceedingly rare

The cases that have occurred in Florida weigh strongly with those who maintain that attenuated vaccines should be reserved for areas where the majority of adults are naturally immune, and that in other areas, where there are still susceptible adults who are particularly vulnerable to paralytic infection, inactivated vaccine should be used Sabin's strains, which, of those now available, are clearly the most attenuated for monkeys, have been extensively used in Russia, and the Russians are quite convinced that they are safe for both children and adults Some doubts have been expressed as to whether adequate numbers of adults without antibodies have been studied even with Sabin's strains to establish safety in these particularly vulnerable people These doubts are caused mainly by the incidents in Florida and West Berlin with Cox's strains leading to fears that Sabin's strains have not been tested adequately in a comparable population Rumours that in Russia cases occurring within twenty-one days of vaccination have been ignored in the assessment of efficacy and safety have not allayed these fears[5] Fortunately, however, this view of the Russian work is not supported by PAYNE nor by HORSTMANN, who have analysed the methods and results In vaccinated individuals there have been a few cases of poliomyelitis which could have been due to vaccine, just as cases sometimes occur after administration of killed vaccine, but these have not been concentrated in such a way as to implicate the vaccine The conclusion that Sabin's strains have so far proved safe for the vaccinated seems to be warranted, but the importance of spread to contacts remains undecided This undoubtedly can occur, but its frequency varies from population to population Thus spread is especially likely in summer, in conditions of poor hygiene, and in young children, and its likelihood is reduced in winter, in adults or children over 2 years, and in upper socioeconomic groups In FOX's careful studies in Louisiana the attenuated strains have been found to spread less readily than naturally occurring wild strains This leads Fox to believe that fears about reversion to virulence may be academic Such reversion probably does take place to levels of neurovirulence for monkeys which would be unacceptable in a vaccine strain Reversion almost certainly occurs in the field, and has been clearly shown in the laboratory But the field studies have rarely been made under conditions where naturally occurring poliovirus has been excluded and the progeny of the ingested vaccine strain has been recovered Although the importance of reversion to virulence may have been over-emphasised, an ideal attenuated vaccine strain should be genetically stable—although this is almost certainly asking for the impossible Unfortunately, the present Sabin type-3 strain is notoriously unstable

One other factor concerning safety is the presence of viruses in the monkey-kidney cells used to propagate the vaccine viruses At the Washington meeting SWEET and HILLEMAN[6] described a new agent present in many cynomolgus or rhesus monkey-kidney cultures which only produces complete destruction of the cells of

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[1] See *Lancet*, 1960, i 1057
[2] See *ibid* Aug 6, 1960, p 311
[3] Kirchstein R., Baron, S Borman G S, Murray, R, Perkins, F T, Hottle, G *Virology*, 1960, 11 300
[4] Sabin, A B, Ramos-Alvarez, M Alvarez-Amezquita, J, Pelon W, Michaels R H Spigland I, Koch, M A, Barnes, J M., Rhim, J S *J Amer med Ass* 1960, 173, 1521
[5] *Brit med J* July 16, 1960 p 202
[6] Sweet, B H, Hilleman M R. Paper presented at the 2nd International Conference on Live Poliovirus Vaccine, Washington, 1960

African monkey kidney (especially *Cercopithecus aethiops*). This agent, called vacuolating virus, is present in Sabin's seed virus, but it has not been isolated from the fæces of vaccinated persons, nor have antibodies been found in the few people who have been tested after receiving Sabin's vaccine. On the other hand antibodies to this agent have been discovered in people who have received killed adenovirus vaccine prepared in monkey-kidney cultures. The significance of this new agent is not so much that it is likely to be *immediately* lethal to man, as that it demonstrates an unsatisfactory ignorance of what other living agents may be present in a living virus vaccine grown on potentially contaminated cells. The solution to this problem may be, as KOPROWSKI has suggested, the use of cells which have been maintained in the laboratory for some time without a change in chromosome pattern. Thus cells can often be propagated in the laboratory for some months before undergoing the extensive chromosomal and metabolic changes that give rise to fears of malignancy. Such cells could be extensively tested for known viral contaminants before being used for production of attenuated-virus vaccine. The advocates of living vaccine, with the practical problem of preventing poliomyelitis before them and the impressive experience in Russia and elsewhere [5] behind them, believe that any remaining doubts reflect excessive caution. The glittering prospect they see is the elimination of poliovirus from the world. Nevertheless safety has not yet been clearly established in a country with non-immune adults, and the high hopes of efficacy remain to be fulfilled. It is, for example, already clear that one dose of each type formerly thought adequate is not going to prove sufficient.

In countries of Western Europe and North America where killed poliovirus vaccines have been used the results have been, in general, excellent. Effectiveness against proven poliomyelitis almost certainly exceeds 90%, and may be 95% or more following three doses. Some problems, however, remain: the vaccine is insufficiently potent and some failures occur, at least three doses are required (probably more for persistent immunity), and vaccine acceptance has been less good than was hoped. In 1958 in Massachusetts, according to LANGMUIR,[2] the vaccine had little or no effect against type-3 poliovirus. Since this unfavourable experience was confined to the State of Massachusetts, it may have been an isolated incident due to some accident to the vaccine. But the type-3 component of the American vaccine is not very antigenic, and, as LANGMUIR says, this experience may be a warning of future trouble. Furthermore present vaccines contain extraneous protein (albeit in very much smaller amounts than in many other prophylactics) and antibiotics which may cause trouble. At the Copenhagen conference HILLEMAN announced the development of purified concentrated poliovaccine which goes a long way towards overcoming these difficulties. The other way in which acceptance of prophylactics could be enhanced is by the development of combined antigens protecting against poliomyelitis, diphtheria, tetanus, and pertussis. Unfortunately a serious difficulty has developed. Since poliomyelitis is severe if contracted in pregnancy, the administration of vaccine to expectant mothers is desirable, but this gives rise to high levels of maternal antibody in the newborn, and these severely inhibit the effectiveness of poliovaccine in the infants.[7] It seems, therefore, that quadruple vaccine is unlikely to be satisfactory unless the increased antigenicity of purified concentrated poliovaccine can overcome maternal antibody, since to be of the fullest possible value pertussis vaccine must be given early in life. Alternatively the pertussis vaccine could be given separately, early in life, and followed at about 9 months by triple antigen to protect against poliomyelitis, diphtheria, and tetanus. If the poliovaccine used was as potent as that described by HILLEMAN, it is almost certain that the only additional booster dose required would be on school entry. In summary, the evidence seems clearly to favour persisting with killed vaccine, preferably of increased potency, in this country at present. More work is also needed to remove the last remaining doubts about the safety and efficacy of Sabin's strains in a population with a significant proportion of non-immune adults. Such work will have received a great impetus from the announcement by the U.S. Surgeon-General that Sabin's vaccine has been found suitable for use in the United States, with the promise of licensing manufacture early in 1961.

Cat-scratch Disease

WHEN the bite or scratch of a cat is followed by subacute inflammation of the regional draining lymph-node, with or without suppuration, cat-scratch disease may be considered and a skin test applied to confirm the diagnosis. The condition is an infection of unknown ætiology, uncertain epidemiology, protean clinical features, and unpredictable natural history, and there is no specific therapy. It is apparently distributed widely throughout the world. Originally described a decade ago in France,[8] it has since been recorded in several other countries, including Great Britain,[9] [10] South Africa,[11] the United States,[12] [13] and Canada.[14] DANIELS and MACMURRAY [13] drew attention to 160 cases observed in the United States and eight other countries, and to this large series may now be added 83 cases recorded by SPAULDING and HENNESSY from Toronto.[15]

In Toronto the disease presented most often in the winter months. This was not a single epidemic, for the series was observed over a four-year period. In roughly the same four-year span, cat-scratch disease was tentatively diagnosed on 13 occasions in South Africa.[16] It would be interesting to learn whether the South African Institute for Medical Research noted a seasonal variation as in Nova Scotia [14] and Toronto,[15] for the two continents have such different climates. This finding might influence the only present hypothesis concerning the seasonal distribution—namely, that cats spend longer out of doors in warm weather and humans thereby suffer fewer scratches

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[7] Perkins, F T, Yetts, R, Gaisford, W *Brit med J* 1958, ii, 68
[8] Debré, R., Lamy, M, Jammet, M L, Costil, L., Mozziconacci, P *Bull Soc méd. Hôp Paris* 1950, 66, 76
[9] Brand, T A, Finkel, K C *Brit med J* 1956, i, 88
[10] Lyon, R L *Lancet*, 1956, ii, 555
[11] Dreosti, A E, Murray, J F *S Afr med J* 1953, 27, 81
[12] Greer, W E R, Keefer, C S *New Engl J Med* 1951, 244, 545
[13] Daniels, W B, MacMurray, F G *J Amer med Ass* 1954, 154, 1247
[14] Marshall, C E *Canad med Ass J* 1956, 75, 724
[15] Spaulding, W B, Hennessy, J N *Amer J Med* 1960, 28, 504
[16] Marshall, J *S Afr med J* 1960, 34, 493

In the Canadian series, besides an almost invariable history of contact with cats, there was evidence of scratches in over half the cases An incubation period of 7 to 61 days was followed by indolent granulomatous lymphadenitis in various superficial lymph-nodes—principally axillary (32 cases), cervical (17), inguinal (15), or multiple sites (15)—with subsequent suppuration after about a month in 26 of the 83 cases If suppuration did not appear within 6 weeks, then it was unlikley to do so Fever and constitutional symptoms were common but not invariable, and associated clinical features included arthralgia, phlebitis, paronychia, splenomegaly, erythema nodosum, and encephalitis These inconstant accompaniments are of little help in the clinical diagnosis and may even prove confusing, for each of these features has commoner causes The differential diagnosis is that of subacute lymphadenitis and varies with the site cervical lymphadenitis, having so many causes, is particularly perplexing A specific skin test is at present the most reliable means of confirming the diagnosis Antigen is prepared from human lymph-node pus, very much as Frei antigen was made, and somewhat as Kveim antigen is prepared Intradermal injection of 0 1 ml cat-scratch antigen causes a tuberculin-like delayed hypersensitivity reaction in 48 to 72 hours in those who have or have had cat-scratch disease As with most skin tests of this type, occasional false-negative and false-positive reactions ensue With strong clinical evidence of the disease a negative skin test should not be accepted as such until other batches of antigen have been tried, for not all batches of this crude human antigen are potent False-positive reactions are difficult to interpret, for control reactors may previously have sustained trivial, undiagnosed infection 3 positive reactors to the skin test were found by BETTLEY and FAIRBURN[17] in a group of 40 control adults in London, and 3 by SPAULDING and HENNESSY[15] in a control group of 100 nurses and medical students

Since no causal agent has been identified, specific serological antibodies cannot be detected Instead, complement-fixing antibodies to lymphogranuloma-venereum antigen have been noted in a minority of patients—notably adults[15 18] This has suggested that cat-scratch disease may belong to the psittacosis/lymphogranuloma-venereum/trachoma group of diseases, but proof has been impossible because attempts to isolate the causal organism of cat-scratch disease in laboratory animals or chick embryos or by tissue culture have been fruitless, and skin tests with lymphogranuloma antigen in patients with cat-scratch disease are nearly always negative In Toronto, the lymphogranuloma-venereum complement-fixation test was positive in 14 of 39 patients, mostly adults, and it was negative in 120 control adults, thus, when positive, this test provided some support for the diagnosis Other inconstant alterations in the blood include leucocytosis, lymphocytosis, monocytosis, eosinophilia, and increased erythrocyte sedimentation[15] Antibiotics have had no consistent effects on the course of the disease, and a fluctuant abscess is best treated by closed aspiration in order to avoid a persistent discharging sinus

Many problems remain unanswered—not the least being the role of the cat Recurring sporadic infections in households where the cat has remained in good health suggest that it is a healthy carrier, but how it harbours the infection is unknown To cast this household pet as the villain of the piece may seem uncharitable, and in any event much further evidence must accumulate before a cat-loving nation will consider banishing the animal out of doors

Newtonian Physic

THE mechanical forces acting in a closed head-injury are still disputed The original conception of forces acting in straight lines from the point of impact is now recognised as wrong The important forces are those of rotation, as can be readily demonstrated with a flask of water containing some flecks of sediment HOLBOURN[1] described the stress and strain consequent on rotational forces, which he illustrated with a gelatin model transilluminated with polarised light. PUDENZ and SHELDEN[2] made movements of the brain visible through a " calcarium " made of clear plastic The sites of stress corresponded with known sites of damage in severe head injuries, and also with symptoms in terms of accepted physiology But one important matter has not been satisfactorily settled Whereas JEFFERSON[3] and others emphasised disturbed function of the brain-stem in concussion, DENNY-BROWN and RUSSELL[4] considered that function in most if not all of the brain became disordered by reason of *commotio cerebri* Subsequent discoveries regarding the reticular formation and other diffuse projection systems seem to support JEFFERSON's view and also to explain the widespread loss of function The frequency of damage to the frontal bases and temporal poles accords with the frequency of temperamental and vasomotor instability in the post-traumatic period

DENNY-BROWN and RUSSELL[4] showed that acceleration (including negative acceleration or deceleration) is enormously more productive of concussion than a blow to a head that cannot move DOTT[5] now emphasises that a further factor is deformity of important perforating vessels The character of the striking object and the site and direction of the impact partly determine any injury to the cranium[6], and LINDENBERG and FREYTAG[7] conclude that the site of any fracture of the skull influences cerebral injury, that mass movement even by small distances is more important than pressure waves without mass movement, and that rotation cannot well explain "contre-coup" lesions, which are generally located according to the direction of the force of impact They thought that in severe injuries contralateral pressure is not negative but positive[8] and that the result is herniation at the foramen magnum, and in support they cited hæmorrhages in the cerebellar tonsils and medulla oblongata Their material, however, was derived entirely from postmortem examination, in many of their cases the injury went far beyond the minimally mortal, and they produced no argument which invalidates present ideas on simple concussion,[9] and even fatal concussion and "contusion", from rotational forces

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[17] Bettley, F R., Fairburn, E. A. *Lancet*, 1953, i, 520

[18] Armstrong, C, Daniels, W B MacMurray, F G., Turner, H C. *J Amer med Ass* 1956, 161, 149

[1] Holbourn A H S *Lancet*, 1943, ii 438

[2] Pudenz, R. H , Shelden, C. H *J Neurosurg* 1946, 3, 487

[3] Jefferson, G *Glasg med J* 1942, 20, 77

[4] Denny-Brown D , Russell, W R *Brain*, 1941, 64, 93

[5] Dott N M *Brit med J* July 2, 1960, p 12.

[6] Gurdjian, E S , Webster, J E Head Injuries London, 1958

[7] Lindenberg, R , Freytag, E *A.M.A Arch Path* 1960, 69, 440

In concussion the crucial factor is acceleration of the moving head If deceleration of a head travelling at, say, 80 miles an hour can be extended to cover an appreciable fraction of a second, damage will be reduced enormously Motorists are unlikely to wear crash helmets in addition to safety belts, but these might incorporate a cap with a loose-fitting elastic band at the back of the neck

Annotations

TOO FEW DOCTORS?

IN their important article on p 538 Professor Lafitte and Professor Squire conclude that "*Unless there is immediate action, something like a crisis in the supply of* doctors may emerge around 1964 " Questioning some of the Willink Committee's assumptions,[10] and revising the committee's estimates accordingly, they calculate that Great Britain ought to have produced 2100 new doctors each year in 1955–60 and ought to be producing 2060 a year in 1960–65 On this basis the average annual shortfall was 275 in the first of these quinquennia and may amount to 310 in the second Prompt action will be needed, they think, to avert the trouble which may encompass us within a few years

After the Willink Committee reported in 1957, many hard-pressed universities adopted with evident relief its recommendation that the intake of new students should be reduced by about 10% The effects of this reduction have yet to make themselves felt, but shortages from other causes are already evident The difficulty of finding junior medical staff for outlying hospitals is, of course, no novelty, but very few of us can have expected to see the upswing in the average number of patients on the lists of general practitioners The Willink Committee suggested that the maximum list should be reduced without undue delay to 2500 in non-rural areas and to 2000 in rural areas, and the public—so tired of finding that their doctors cannot spare them time—could reasonably expect progress towards this reform But in point of fact the average number of patients has actually risen in England and Wales the average (not the maximum) was 2282 in July, 1959, against 2267 a year earlier[11] The increase of remuneration arising from the Royal Commission's report[12] provided a rare opportunity for reducing the maximum list from the present 3500 for single-handed practitioners and 4000 for partners, and it is therefore profoundly disappointing that the joint working party[13] shoul merely suggest the setting aside of £1 million each year, i the hope that a further working party will consider ho "the best possible general medical service" can b provided Yet the decision to retain large lists is no surprising if there are not in fact enough qualified doctor to take on the patients who would be removed from suc lists Already it is none too easy to fill some vacancies i the less attractive areas, and in England and Wales th average number of applications for each advertised vacanc fell from 43 in 1956 to 35 in 1957, 31 in 1958, and 24 i 1959[14] Admittedly these numbers cannot be taken at the face value on the one hand, often a doctor applies at th same time for more than one vacancy, and the total include applications by those already in practice who wan to move to another area, and, on the other hand, a increasing proportion of would-be entrants to practic may be seeking to join a partnership Nevertheless the consistency and extent of the downward trend is impressive

Lafitte and Squire put their own estimates forward merely as a starting-point for a fresh inquiry But, if they are even partly right, the present signs of shortage must be regarded as straws in the wind If we are not careful they may turn into a positive haystack, blown before a hurricane

MARFAN'S SYNDROME

Sinclair et al,[15] enlarging on the work of McKusick,[16] have again drawn attention to the consideration which should be given to Marfan's syndrome as a possible cause of "idiopathic" cardiovascular disorder Marfan's syndrome is an inherited disorder characterised by dolichocephaly, elongation of the extremities (arachnodactyly) and other skeletal deformities, ocular abnormalities (of which subluxation of the lens is the commonest), and often cardiovascular abnormalities[17] Probably there is a single underlying biochemical defect[18], and, if this is so, it seems likely to involve the structure of elastic tissue, leading to some disorders which are congenital, and to others which appear in later life as a result of strains and stresses on the tissues involved

Sinclair et al suggest that in this syndrome dilatation of the pulmonary artery, the aortic ring, the sinus of Valsalva, and the aorta, and rupture of the aorta with or without a dissecting aneurysm result from cystic medial necrosis Deformities of the valve cusps with murmurs they regard as a consequence of myxomatous degeneration They do not, however, advance an explanation for the arrhythmias which may occur, and they consider that such abnormalities as atrial septal defect and patent ductus arteriosus are not intrinsic parts of the syndrome Certainly when any of these cardiac abnormalities are found and cannot be otherwise explained, the other features of Marfan's syndrome should be sought, for minor skeletal defects are not always immediately evident The shoulders may be abnormally wide, the pelvis narrow, the span of the outstretched arms greater than the height by more than three inches, and the length from pubis to heel greater than that from vertex to pubis by more than two inches These deviations are not uncommon with an otherwise normal physique

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[8] Gurdjian, E S, Lissner H R, Latimer, F R, Haddad, B F, Webster, J E *Neurology*, 1953, 3 417

[9] Russell, W R *Brit med Bull* 1954, 10 65

[10] Report of the Committee to Consider the Future Numbers of Medical Practitioners and the Appropriate Intake of Medical Students H M Stationery Office 1957 See *Lancet*, 1957, ii 1043 1057

[11] Report of the Ministry of Health, 1959 part I, p 75 H.M Stationery Office 1960

[12] Royal Commission on Doctors and Dentists Remuneration 1957–60 Cmnd. 939 H M Stationery Office, 1960 See *Lancet*, 1960, i, 421, 427

[13] See *Lancet* Aug 27, 1960, p 482

[14] Report of the Ministry of Health, 1959 part I, p 77

[15] Sinclair, R. J C, Kitchin, A H, Turner, R W D *Quart J Med* 1960, 29, 19

[16] McKusick, V A *J chron Dis* 1955, 2 609, *Circulation* 1955, 11, 321

[17] Marfan, A. B *Bull Soc méd Hôp Paris*, 1896, 13 220

[18] Sjoerdsma, A., Davidson, J D, Udenfriend, S, Mitoma, C. *Lancet*, 1958, ii, 994

Arachnodactyly, originally named by Achard,[19] has long been considered a most useful clinical feature in the diagnosis of this condition But, as Sinclair et al point out, long fingers may be a feature of an otherwise normal family, or may even be merely the subjective impression of the observer They therefore propose the use of a "metacarpal index" The lengths of the right second, third, fourth, and fifth metacarpals as seen on a radiograph are measured and the breadth of each metacarpal at its exact midpoint is also measured A figure for each metacarpal is reached by dividing the length by the breadth, and the average of the four is taken Sinclair et al claim that the normal range is from 5 4 to 7 9, whereas in Marfan's syndrome the range is from 8 4 to 10 4 Thus, if these findings are confirmed, an index greater than 8 4 is diagnostic of arachnodactyly Estimation of this metacarpal index is simple, and if it is found to be positive, more detailed skeletal measurements and ocular examination should be undertaken

Marfan's syndrome is a cause of premature death, and diagnosis in a patient should be followed by a detailed survey of his family Such surveys may add to knowledge of the frequency and mechanism of inheritance of this condition

BENIGN POLYARTHRITIS

THE sheep-cell agglutination test, with its high degree of specificity for rheumatoid arthritis, has been valuable in helping to establish the separate identities of such conditions as ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, and the arthritis of ulcerative colitis, in which it is nearly always negative This test has been used in a recent study by the Empire Rheumatism Council field unit[20] of a form of arthritis about which little has been written, but which is apparently common.

In a previous rheumatism survey[21] it was found that of 380 persons aged 55–64 years, 36 gave a past history of transient incapacitating inflammatory polyarthritis In the latest study Lawrence and Bennett[20] surveyed a random population sample in the same town (Leigh, Lancashire), including all ages from 15 years onwards Altogether 1343 selected persons (653 males and 690 females) were questioned with particular reference to joint symptoms, and were examined physically, by joint radiography, and by the sheep-cell test. A past history of polyarthritis was encountered in 34 (5%) males and 50 (7%) females 7 males and 15 females (26% of those with a history of polyarthritis) showed clinical or radiographic evidence of residual arthritis Clinical residua included metatarsophalangeal and interphalangeal joint subluxation and pain or limitation of movement of metacarpophalangeal joints, wrists, knees, tarsal joints, and cervical spine. 3 patients had frank rheumatoid arthritis Radiographic residua, found mainly in the cervical spine, resembled those of rheumatoid arthritis in that the upper vertebræ were affected more than the lower, but subluxation was less and degenerative changes were greater than is usual in rheumatoid arthritis Sacroiliac joints were normal The sheep-cell test was positive in only 2 (6%) males and 4 (9%) females with a past history of polyarthritis, which is not significantly different from the figures of 5 and 6% in the males and females without polyarthritis A history of cardiac involvement at the time of the attack was given by 14 persons, but clinical evidence of mitral stenosis was found in only 4 The onset occurred at any age, but was commonest between 5 and 24 years—a distribution which is similar to that of rheumatic fever There was a striking seasonal distribution of attacks, onset being commonest in the winter months Attacks were usually single, lasting two or three months, but up to eight recurrences in one person were noted.

The nature of this benign polyarthritis is unknown, but it seems unlikely to be a single disease Some of the cases were surely of rheumatic fever, but the joint residua are not those described in the "Jaccoud type" of chronic polyarthritis,[22] said occasionally to follow repeated attacks of rheumatic fever (little is agreed about this syndrome except that it is rare) Other cases may be of rheumatoid arthritis The sheep-cell-agglutination test was positive in only 7% of all with a history of polyarthritis, but the ætiology may be similar to that of rheumatoid disease, the high proportion of negative sheep-cell tests being related to the benign course of the condition—a poor prognosis seems to be related in rheumatoid arthritis to a positive sheep-cell titre In such a retrospective study the titre at the time of the attack cannot be established, but Lawrence and Bennett point out that in patients with rheumatoid arthritis the titre changes in both directions, and they suggest that had an appreciable proportion of patients been sheep-cell positive during the attack there would have been a significantly higher proportion of positives in the polyarthritics than in the remainder of the population Some of the patients who had had attacks in childhood may fall into the category of Still's disease, but although the benign prognosis is not inconsistent with this diagnosis the acute transient nature of the arthritis is not characteristic of Still's disease Finally, the seasonal onset suggests a winter infectious disease Little is known of acute polyarthritis in relation to virus diseases though the arthritis of rubella is well documented[23]

The patients in this series were almost all treated at home, and benign polyarthritis is not often seen in hospital practice. Prospective surveys will in time no doubt add to our scanty knowledge of the condition Useful descriptive studies may be expected to come from general practitioners, who are best placed for this task.

MEAT INSPECTION

IT is no secret that a good deal of meat killed in England and Wales is not inspected by certificated public-health inspectors as the Law demands. To save labour, the number of slaughterhouses was reduced during the war, but in 1951 this policy was reversed and it was not (and is not) difficult to obtain authority to slaughter in suitable premises anywhere. (Shortly after this change of policy a Government committee recommended a rational distribution of large modern slaughterhouses and the closure of all the smaller ones, but unfortunately this suggestion has had little support.) The number of licensed slaughterhouses in the districts devoted to cattle-rearing is astonishing—e g , 32 in a rural district ten miles square, and many of them at the back of beyond. Some are used every day, some twice a week, and some only once a month It is no wonder that the public-health

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[19] Achard, C. *Bull Soc méd Hôp Paris*, 1902, 19 834
[20] Lawrence, J S , Bennett, P H *Ann rheum Dis* 1960, 19, 20
[21] Kellgren, J H , Lawrence, J S *ibid* 1956 15, 1
[22] Bywaters, E G L *Brit Heart J* 1950 12, 101
[23] Johnson, R E, Hall, A P *New Engl J Med* 1958, 258, 743

Special Articles

SECOND THOUGHTS ON THE WILLINK REPORT

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FROM February, 1955, to August, 1957, the Willink Committee, appointed by the English and Scottish Health Departments, attempted "to estimate, on a *long-term* basis the number of medical practitioners likely to be engaged in all branches of the profession in the future, and the consequential intake of medical students required" They decided, not unreasonably, that long-term estimates were impossible There were too many "uncertainties and imponderables" which they could not assess They felt unable to look beyond 1971 The output of doctors was already determined up to 1961 by the number of students already admitted to medical schools Their report (November, 1957) was therefore chiefly concerned with policy during the decade 1961–71

They concluded that a reduced output of doctors would suffice after 1961 Student intakes should in consequence be reduced "by about a tenth from as early a date as is practicable" But they surmised that from about 1975 a greater output was likely to be needed Recruitment of medical students would therefore have to be raised from about 1970 This latter conclusion was, however, very speculative, and they prudently recommended a fresh review of the situation round about 1967

The somewhat scrappy statistics of admissions to medical schools clearly show that the authorities have acted on the committee's advice The apparent annual recruitment of medical students in England, Scotland, and Wales fell from 2741 in 1955–6 to 2504 in 1958–59, mainly by the recruitment of fewer women students[1] Allowing for double counting (which the authorities still fail to exclude from their figures) it looks as if the real intake in 1958–59 was about 2030 students, against perhaps 2220 in 1955–56 The reduction is of the order prescribed The Willink policy is in force The University Grants Committeee feel bound by it when considering financial requests from medical schools Full-time medical students dwindled from 13,340 in 1955–56 to 12,700 in 1957–58 The Willink policy will soon bring them down to 12,000, very little more than their total in 1938–39 and far below the post-war peak of 14,200

The purpose of this article is to challenge the assumptions of present policy, to show that some of the Willink Committee's key calculations have been falsified by events, to argue that, if policy is not reconsidered, there is likely to be underproduction of doctors, to indicate broadly, using the committee's own methods, what the reasonable medical manpower requirements of the coming decade may well amount to, and to urge that a fresh and more searching inquiry be instituted now, not in 1967 If the position is as urgent as appears, some action should indeed be taken almost at once by the universities and the U G C in order to avert the troubles which may otherwise be inescapable from about 1965 onwards

TABLE I—ANNUAL NUMBERS OF NEW DOCTORS REQUIRED GREAT BRITAIN

—	Willink estimates			Revised estimates		
	1955–60	1960–65	1965–70	1955–60	1960–65	1965–70
Export	160	110	70	160	110	70
Forces	55	55	55	55	55	55
Wastage	1150	1150	1230	1290	1320	1300
Expansion	465	410	280	627	602	491
Totals	1830	1725	1635	2132	2037	1916

Assumptions and Implications

The Willink findings can be criticised along two different lines First, some of their basic assumptions may be challenged (e g, about standards of medical care in an emerging affluent society) Second, other assumptions may be accepted (e g, about doctor/population ratios), but with their implications recalculated in the light of *current statistics*

Under the first heading the main consideration is that, as prosperity advances, a growing proportion of the population will demand a "middle-class" standard of medical care, for which the committee made scant allowance Though we attach considerable weight to this "imponderable", our main object is to demonstrate that, on the committee's own assumptions about the overriding importance of population trends to the need for doctors, their estimates of future requirements need extensive upward revision This is because the committee used official population projections which have been falsified by events They concluded that over 1955–71 the increase of population would amount to about 4½% In our Appendix we attempt to show that policy cannot safely reckon with less than an 8% increase over 1955–70

If this had been the prospect placed before the Willink Committee, and if they had retained most of their other leading assumptions, would they still have proposed cutting the medical schools' intake by a tenth for a whole decade? We believe they would in fact have ended up with something like the revised estimates shown in table I Unless these revised figures are badly at fault, they are an argument for renewed expansion, not contraction

In these revised estimates we have not altered the committee's figures for "export" of doctors or for the needs of the Forces Nor, save for hospital staffing after 1965, have we raised any of their figures to allow for any improvement in standards of medical care beyond what they themselves assumed For these reasons the revised estimates probably understate the requirements of the next ten years

Though we have retained the committee's export figures, we question their belief that there will or should be a substantial fall in the number of British doctors going to other countries during the next decade The growth of medical and educational facilities within the Commonwealth cannot always keep pace with extensions of political independence—at least not without considerable help from Britain The needs of the Commonwealth's underdeveloped territories are indeed such that there is a powerful case both for enlarging British medical schools to take in more Commonwealth undergraduates and postgraduates and for maintaining or increasing "exports" of British teachers and practitioners

Wastage

From a count of the British Medical Association's medical man-power register and from the proportions of doctors recorded as occupied or retired at the 1951 census, the committee concluded that doctors in Britain were distributed as follows

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[1] University Grants Committee annual returns, H M Stationery Office

	Active	*Retired*	*Total*
Male	36,660	5200	41,860
Female	8300	3100	11,400
Total	44,960	8300	53,260

The active doctors included those giving only part-time or occasional service No less than 69% of male doctors aged 65–69 were regarded as active, as well as 37% of those over 70 In reckoning for the committee the future numbers needed merely to replace the doctors of 1955 (as they die, retire, or migrate), the Government Actuary assumed that the proportion of male doctors aged 65–69 who were active would slowly decline to 35% by 1988 and the proportion active after 70 to 15%

How realistic was this calculation? In 1955, on the committee's reckoning, 6 8% of active doctors were over 65 Early in 1958, according to the Pilkington Commission's survey,[2] the over-65s formed only 0 3% of all active consultants, rising through other branches of medicine to 5 6% of active general practitioners—active here meaning participating even to a minimal extent in the National Health Service (Very few doctors are wholly engaged in private work) All these figures refer to periods before doctors could first qualify for N H S superannuation benefits "One or two of our witnesses", said the committee, "did not dissent" from the view that "the average doctor is sufficiently attached to his profession to wish to continue in practice as long as his health and energy will allow" The Government Actuary was therefore asked to allow for only a slow trend towards earlier retirement among superannuable doctors

Since then, the statistics of principals giving unrestricted general medical service in the N H S in England and Wales supply a foretaste of future trends The number of these doctors aged under 66 grew from 18,242 in 1958 by 200 to 18,442 in 1959, but the number over 66 dropped sharply from 1357 by 145 to 1212 The change is officially ascribed to the coming into force of superannuation from July, 1958 [3] Doctors in the hospital service are normally expected to retire at 65 And the Government Actuary himself has lately assessed the probability of retiring within twelve months after age 64 at 0 9889 for hospital doctors and 0 9823 for general practitioners [4] This can hardly be reconciled with the committee's assumption that even in 1988 over a third of such men under 70, and nearly a sixth of those over 70, will still be "active"

We propose to assume that, of the elderly doctors the committee expected to find still on the active list, four-fifths will in fact be active in 1960, two-thirds in 1965, and half in 1970 In that case the number of doctors to be replaced, simply to maintain the 1955 total, compares with the Willink estimates as follows

Year	*Willink assumptions*	*Revised assumptions*
1955–60	5520	6155
1960–65	5430	6070
1965–70	5770	6060

To derive from these quinquennial wastage totals the average annual number of newly qualified doctors needed for replacement, the Government Actuary (a) assumed that the numbers of men and women entering practice "will be such as to accord with the ratio of 4 1 on entry to the medical schools", and (b) assumed that wastage between qualifying and entering practice (and apparently during training) will be as hitherto (The report estimates that 99% of men qualifying and 85% of women qualifying enter practice, and that 4 8% of male, and 8 5% of female, medical students drop out before qualifying) Assumption (a) is questionable The sex ratio on entry to medical schools (not adjusted for duplication) appears not to have been four men for each woman but to have ranged from 3 12 1 in 1954–55 to 3 53 1 in 1957–58 A future entry ratio of 3 6 1 at the most is more likely than 4 1 Applying assumption (b) to this ratio, and adjusting the wastage figures accordingly, we arrive at the revised annual figures for replacement of wastage shown in table I

Expansion

It is difficult to follow the "expansion" estimates of the report, because much of the committee's arithmetic and its underlying assumptions are concealed

1 Some of the minor calculations are intriguing No increase whatever was allowed for the whole-time medical staff of the Medical Research Council (which in fact grew from 177 in October, 1955, to 222 in October, 1959) or for doctors engaged in full-time postgraduate study or research Whole-time university medical teachers and research-workers (other than those with hospital contracts) were allowed to increase by 12 a year (or 1%)—an admittedly "speculative" figure The pharmaceutical industry was supposed to recruit 40 full-time and 10 part-time doctors during 1955–60 and then to cease enlarging its medical staffing In the whole range of industrial medical services there was room for only 45 additional doctors a year up to 1960 and for 20 a year hereafter These estimates reflect a depressingly "realistic" attitude to medical research and to industrial health They fall short of the nation's needs and may even have fallen short of actual trends since 1955

2 The committee proposed a few once-for-all increases to remove certain acknowledged deficiences They allowed for certain declared public vacancies—140 in Government medical services and 125 in local-authority services "The effect, if any, of population changes on the numbers of doctors employed by local authorities (including those employed in the School Health Service) will be small" For general practice the committee did postulate an appreciable improvement in standards They allowed for the doctors needed to reduce average practice sizes to 2500 in those non-rural areas, and to 2000 in those rural areas, where larger average lists prevailed They concluded that these under-doctored areas needed another 625 doctors But they contemplated no improvement beyond this They did not, for instance, examine the implications of reducing average-list sizes in all non-rural areas to, say, 2200 (these areas averaged just over 2350 patients per doctor in England and Wales in 1959 [5]) or of applying the doctor/population ratio of "well-doctored" areas to the rest of the country

3 The committee's main expansion estimates derive directly from their assumption of a $4\frac{1}{2}$% population increase over sixteen years In fact, by 1959, population had already grown by 2%, and, as is argued in the Appendix, trends since 1955 point to an increase of the order of 8% by 1970 The committee allowed 75 extra general practitioners a year for population growth and ageing, though how much was allowed for each factor is not clear Over sixteen years this amounts to 1200 doctors, or 5 6% of the general-practitioner strength of 1955 Allowing the old people 70% more family-doctor consultations

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[2] Statistical Supplement (Cmnd 1064) to Report of Royal Commission on Doctors and Dentists Remuneration H.M Stationery Office, 1960

[3] Ministry of Health annual report for 1959 part I, pp 74–75 H.M Stationery Office, 1960

[4] Report on N H.S Superannuation Scheme, 1948–55 H.M Stationery Office, 1959

[5] Ministry of Health report (ref 3), app XVII

than the average for younger ones,[6] an 8% population increase which includes a 25% increase of the old implies a 10% rise in need for general-practitioner care. This amounts to 2134 additional doctors, or 142 a year—a near doubling of the Willink figure.

What has actually happened to the supply of general practitioners since 1955 is not wholly clear. If spread over sixteen years (the Willink Committee in fact spoke of reducing over-size lists "over the next few years"), the committee's requirements for England and Wales come to 105 extra doctors a year, while our estimate would be 165. From 1955 to 1959 the increase of principals in the N.H.S. in England and Wales (the series used by the committee) has averaged 232 a year. But there has also been an average annual decrease of 51 assistant general practitioners (the number of which the committee kept static), so that the net annual increase has averaged 181 doctors. Notwithstanding this advance, in "designated" and "intermediate" rural areas combined, doctors' lists averaged 2189 patients in 1959 against 2136 in 1955, and the patient population of these areas has grown from 7.36 million to 7.72 million. In "designated" non-rural areas, while the patient population fell from 9.42 million to 8.37 million the average list was virtually as large in 1959 (2743) as in 1955 (2747), and, compared with 1958, there were signs of deterioration in 1959.[5] The Willink doctor/population ratios are still far from being attained.

4. The committee's estimates for hospital staffing also took account of the effects of population increase, as well as of the likelihood that the demand for specialists will grow "as medical knowledge and practice develop and become more elaborate, exhaustive and time-consuming." The rise in outpatient work was noted, as also the prospects of more hospital building. But the committee thought that the initial rapid expansion of hospital staffs was slackening as "many of the more urgent needs have now been met and ... the spreading of hospital and specialist services beyond the large cities and throughout the country is now well advanced." They concluded that for 1955–65 an annual increase of 320 hospital medical staffs (half juniors and half consultants or senior hospital medical officers) would be reasonable. Although it was "difficult to see further ahead", for 1965–71 they arbitrarily halved these figures to an annual increase of 160. Over 1955–59 this postulated rate of expansion has not in fact been accomplished. The average annual rate of growth has amounted to 292 doctors, not 320,[7] nearly five-sixths, instead of a half, of the increase has occurred among doctors not classified as seniors, and staffing deficiencies are emerging in several regions.

Even granting the committee's other assumptions to be valid, their figures need to be adjusted to a higher rate of population growth. This cannot be done with certainty, both because the committee's own methods are unknown and because of the inherent difficulty of relating hospital requirements with population trends. The committee's demographic assumptions implied, *ceteris paribus*, a 14% increase of inpatients by 1971, while our own assumptions imply a 16½% increase by 1970.[8] Should the need for hospital doctors be assumed to rise in proportion? The committee plainly did not think so. If they had, they would have postulated a "demographic" requirement of 173 hospital doctors a year, whereas for 1965–71 their total requirements for all hospital purposes was only 160 a year. The future pattern of demand for inpatient services may indeed be more influenced by social factors and by policy (e.g., on "community care") than by population trends. And when assessing the need for doctors, trends in outpatient services and in diagnostic and other procedures, as well as in scientific knowledge, all come weightily but imponderably into the picture. All that seems certain is the fact that the growing numbers of the old will make the need for hospital-based doctors grow faster than the need generated by additional population in other age-groups. If policy assumes an 8% population increase over 1955–70, it might be unwise to assume less than a 12% increase in "demographic" demand for hospital doctors. Our revised estimates therefore allow for an annual increase of 157 doctors over the whole period, simply to accommodate demographic needs. A plausible guess at what the committee allowed is that it applied the same factor as for the general practitioners. Taking that as a 5.6% increase over sixteen years, the committee's estimates would include an annual "demographic" quota of 62 hospital doctors. The difference between that figure and our own is 95. This has been added to the committee's totals for expansion requirements in our revised estimates in table I. The effect is to raise the annual requirement for hospital doctors in 1955–65 from 320 to 415 and in 1965–70 from 160 to 255.

But it is far from clear why the committee should have arbitrarily halved its estimates for the period after 1965. Quicker throughput of inpatients and greater concentration on outpatient work do not in themselves reduce the numbers of doctors needed. In some directions, possibly in mental health, they may even enlarge the numbers needed. If the expansion envisaged by the committee for 1955–65—much of it being intended to remove deficiencies—had been fully realised, and if their assumptions about population had been nearer the mark, an appreciable relaxing of pressure to expand could certainly have been reckoned with after 1965. But events have departed a good deal from what was planned. The hospital service will be farther from satiety in 1965 than the committee imagined, and they themselves stressed that their estimates for 1965–71 were "very speculative." To halve the "non-demographic" element in estimated requirements after 1965 seems unwarranted. At least half the cut should be restored, and our revised estimates add 49 to the committee's figures for 1965–71 to allow for this.

In summary, it seems justifiable to raise the Willink figures for "expansion" by adding 67 general practitioners and 95 hospital doctors a year to cover demographic changes, and by assuming that the requirements for hospital doctors for reasons other than demographic will run in 1965–70 at three-quarters, not half, of the hoped-for level in 1955–65.

Discussion

The revised estimates could have been put higher. The Willink Committee could be criticised, for instance, for deliberately ignoring (beyond a certain point) the fact that in a dynamic economy long-range planning cannot proceed on static assumptions. If the "affluent society" progresses at anything like the 2% to 3% compound annual increase in productivity which economists and politicians believe to be likely, then the community will develop both the resources and the appetite for improved standards of medical (including psychiatric) care The fact that medical care is collectively provided and paid for through taxation is irrelevant Advancing prosperity creates the taxable capacity to pay for medical improvements without raising the level of taxation Yet the committee decided that economic advance was one of those uncertainties which are so unpredictable that it had best be left out of account altogether Since they were appointed, the real level of personal consumption per head of population has grown by 7% It is likely to continue rising at least at some such long-term average rate It is quite unrealistic to prepare long-range policies on the assumption that the standard of living *may* be no higher in ten or fifteen years' time than it is now Professor Jewkes is not alone in wondering (in his memorandum of dissent to the Pilkington report)

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[6] This is the ratio suggested by recent surveys—e.g., Logan, W. P. D. and Cushion, A. A., Morbidity Statistics from General Practice, vol. I. General Register Office Studies on Population and Medical Subjects no. 14. H.M. Stationery Office. 1958.

[7] Report of the Royal Commission on Doctors' and Dentists' Remuneration (Cmnd. 939), table 15. H.M. Stationery Office, 1960.

[8] According to the method of calculation used by Abel-Smith, B., and Titmuss, R. M. in The Cost of National Health Service in England and Wales (London, 1956), appendix I.

> "why, although the increase between 1939 and 1958 in the number of full-time university students in Arts of 70 per cent, in Science of 183 per cent, in Technology of 162 per cent, in Dentistry of 93 per cent, and in Veterinary Science of 356 per cent, are all regarded as evidence of social advance, an increase of 7 per cent in medical students in this period is thought adequate, even in an epoch when the demand for medical services and the claims for medical research have so much increased "

Our revised—and admittedly amateurish—estimates will serve their purpose if they establish a prima facie case for a new inquiry But, if they are not wide of the mark, they have some immediate implications for the medical schools and the University Grants Committee The number of full-time students in the medical schools of Great Britain at different dates was

1938–39	11,830	1952–53	13,510	1955–56	13,340
1950–51	14,200	1953–54	13,240	1956–57	12,940
1951–52	13,910	1954–55	13,100	1958–59	12,700

Medical school deans supplied the Willink Committee with figures which showed that the schools' output would average 1825 newly qualified doctors a year (apart from students from overseas) over the seven years from 1955 to 1961 From the figures just given we may infer that the student population needed to sustain such an output is around 13,175, the mean number of students from 1950–51 to 1956–57 If, following the committee, we assume that 30 new doctors a year will be supplied by Northern Ireland, the revised estimates in table I require British medical schools to yield an annual average output of some 2100 new doctors in 1955–60, of 2060 in 1960–65, and of 1885 in 1965–70 This could only be done if doctors in training average 15,220 in 1950–55, 14,880 in 1955–60, and 13,610 in 1960–65 The shortfall of output for 1955–60 is already known The expected annual average is 1825, against our estimate of 2100 needed, giving an annual deficiency of 275 Average numbers in the medical schools in 1959–60 and 1960–61 are not yet known But if they are brought down to 12,000 by the latter year, as the Willink policy implies, then doctors in training will have averaged 12,660 in 1955–60, and doctors produced in 1960–65 will average 1750 a year, showing a deficiency of 310 on our estimated requirement of 2060 a year To make good the shortfalls of these two quinquennia during 1965–70 would require an annual output of 2470 new doctors during those years, and a medical-school population enlarged to average 17,830 over 1960–65

Expansion to such dimensions, to be undertaken forthwith, may well be impossible even as an emergency operation But at the very least these estimates demonstrate that there is no case at all for maintaining the Willink policy, and a very strong case for immediately beginning on an expansion of medical education which plainly ought not to stop in 1965, if even the main part of the requirements we have estimated is to be supplied in ten years' time Unless there is immediate action, something like a crisis in the supply of doctors may emerge around 1965, by which time it will be much harder to deal with

The desirable increase in the intake of medical students looks so large that it may be doubted whether it could be accomplished without the founding of one or two new medical schools in provincial universities The case for founding them is strengthened if the policy of reducing the number of medical students in London, Glasgow, and Edinburgh (as advised by the Goodenough Committee) is maintained Medical schools in these cities have experienced the main reduction of numbers latterly Unless they are re-expanded, or unless some new medical schools are started, the capacity of the remaining centres may be insufficient for what seem to be the requirements of the coming decade In the U S.A , too, doctor supply has been lagging behind population increase Last year the Surgeon General's Consultant Group on Medical Education recommended the creation of 20 to 24 new medical schools, in order to raise the annual output of doctors from 6800 to 10,400 [9] It would be better for Britain to take action before it too has drifted into a situation calling for emergency measures

Summary

In 1957 the Willink Committee suggested a cut in recruitment of students to British medical schools " by about one-tenth " until around 1970 This reduction has been effected But it is now clear that several of the numerical assumptions made by the committee have been falsified by events In particular, population is increasing faster than was expected, and fewer doctors are remaining fully active beyond the age of 65

" Second thoughts " suggest that urgent consideration should be given to expanding medical-student numbers as rapidly as possible from the present 12,000 or so to 15,000 or more At the same time, a fresh and more searching inquiry should be instituted now to redetermine the number of doctors likely to be required in the next decade in all branches of the profession

We wish to thank Dr J A H Waterhouse for helpful discussions, particularly in relation to our Appendix.

Appendix

The Willink Committeee " thought it necessary to make some provision for the fact that the population of this country continues to increase year by year and is steadily growing older " They used for this " the latest published *forecasts* of the Government Actuary " for the period 1955–71 Subsequent demographic events have in fact badly faulted their assumptions Even as they were preparing their report, the Registrars General and the Government Actuary were revising their own *projections* to take account of actual population trends, and they have revised them twice since Each fresh projection has pointed to a higher rate of increase than the last The latest suggests a 7% increase over 1955–71, against the Committee's $4^{1}/_{2}$%—$1^{1}/_{4}$ million more people needing doctors than the committee allowed for

The successive official projections have not altered their assumptions about migration (a minor factor) or mortality We have therefore not changed the Willink estimates in so far as they assumed a 25% increase in the numbers of the old. The official revisions are concerned only with fertility, which each successive revision has so far underestimated The official demographers gave the Willink Committee population estimates which appeared to assume that the total fertility of women aged 15–44, taken as a single group, would decline. Yet in the very year, 1956, when these estimates were issued, even this somewhat crude fertility index rose sharply It has continued rising ever since Moreover, fertility at the most reproductive ages had been rising long before these estimates were prepared There had been an uninterrupted rise since 1952 among women aged 20–24 and, save for a trifling drop in 1954, also among women aged 25–29 Since 1956, women aged under 20 and 30–34 have joined in the rising trend Since over two-thirds of all births occur to women below 30, it would have needed a very large reduction of fertility among those over 30 to bring about that overall decline in the average fertility of women of all childbearing ages on which the Willink sums were based

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[9] See *Lancet*, 1960, i, 275

If the official projections are acceptable as to mortality and migration, but possibly unreliable as to fertility, what assumptions about the coming decade are most appropriate for reconsidering the Willink medical man-power estimates? In table II we present projections for the United Kingdom up to 1970 on three different fertility assumptions, believing that the actual trend will lie somewhere between the first and the third

Assumption A projects the age-specific fertility-rates of 1958 over the whole period 1959–70, and adjusts the official projections accordingly

Assumption B is derived from A, but reduces the fertility of women over 30 by 10% (crudely estimated by taking 3 3% off the birth totals shown in col A)

Assumption C shows the effects of a continuing rise in fertility (linear extrapolation of 1951–58 age-specific fertility rates)

Assumption C shows the upper limit of what is likely It produces a 10% population increase over 1955–70 It carries the annual number of births to over 1 15 million and population increase to 0 5 million a year It accords with the trend of fertility in 1959 and may do so for 1960 as well Yet it seems likely that the fertility increase will stop at some point short of the position shown for 1970, if only because most parents are not likely to want completed families of even the Edwardian size-distribution

On the other hand, assumption A may well show the lower limit of expansion At all ages under 40 fertility has been rising since at least 1956, and at the most fecund ages since 1952 The rise is not the result of transient disequilibria (such as previously deferred marriages or postponed maternities) but seems to reflect a genuine and probably enduring change of family habits It appears to express a growing preference for two, three, or four children over smaller or larger families If so, the rising trend may well slacken to a halt before long But it would not be safe to assume that, for 1960–70 as a whole, fertility will average less than the level of 1958 It will be noted that our inexpert calculations yield population totals identical (allowing for our cruder methods) with those of the official projection The latter, it is understood, though published in terms of an assumed annual flow of births, is reckoned in terms of fertility rates specific both to age and to marriage duration It, too, evidently projects the fertility of 1958

TABLE II—POPULATION ESTIMATES, 1955–70 UNITED KINGDOM

Year	Live births (thousands)				Total population (millions)			
			ACTUAL FIGURES					
1955	789				51 22			
1958	869				51 87			
1959	880				52 16			
			PROJECTIONS					
Year	Official	Assumptions			Official	Assumptions		
		A	B	C		A	B	C
1960	1959-63 annual average 855	851	823	885	52 29	52 29	52 23	52 54
1961		845	817	898	52 50	52 50	52 41	52 79
1962		846	818	919	52 71	52 70	52·59	53·07
1963		851	823	942	52 94	52·91	52 77	53 37
1964	1964–73 annual average 870	854	826	965	53 14	53 11	52·94	53 68
1965		857	828	988	53 56	53 32	53 12	54·02
1966		865	836	1015	53 58	53 53	53 30	54 38
1967		884	854	1059	53 80	53 76	53 50	54 79
1968		897	866	1089	54·03	54·01	53 72	55 22
1969		904	874	1124	54 24	54 26	53·94	55 72
1970		912	882	1154	54 46	54 51	54 16	56 25
			1970 % of 1955		106 3	106 4	105 7	109·9

Sources (1) Actual figures and official projections from *Annual Abstract of Statistics*, 1959, and *Monthly Digest of Statistics*, May 1960 (Official population totals interpolated from figures given for 1963, 1968, and 1973)
(2) Assumptions see text.

In favour of assumption B it may be argued that, if the trend to earlier marriage and maternity continues, and unless the desired size of family continues to rise, women must soon begin greater restriction of childbearing over the age of 30 Even if they did so to the extent of 10% forthwith (they did not in 1959), population increase over 1955–70 would still be around $5^{3}/_{4}$%, against the official $6^{1}/_{2}$% and the Willink $4^{1}/_{2}$% Yet table II suggests that, on present knowledge, assumption B is implausible (e g, actual births in 1958 and 1959 compared with projected births in column B)

We conclude that real population growth over 1955–70 may be expected to occur somewhere between A and C—between increases of $6^{1}/_{2}$% and 10% By 1970 there may be no more old people than the Willink Committee assumed, but between 1 1 million and 1 9 million more younger people Policy cannot be safely tied to any single statistical projection But it would not seem wise to found policy on the assumption of less than an 8% population increase over the whole period—virtually double the growth on which present (Willink) policy of medical recruitment is based

ROBOT ANGIOGRAPHY

A PRELIMINARY REPORT

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THIS note reports work designed to answer the need for (i) accurate timing of the radiographic exposures in peripheral arteriography and (ii) reduction of the dose of radiation to the radiologist, the staff, and the patient This method uses a Geiger counter to detect the arrival of radioactive sodium which is mixed with the contrast medium [1]

In vascular disease the circulation time varies considerably Accurate timing of film exposure is of great value in obtaining maximum vascular filling at different levels of the limbs We thought that injection of a radioactive substance with the opaque medium might enable exposures to be accurately timed Radioactive sodium (^{24}Na), predominantly a γ-emitter, with its short half-life of 15 hours, was used and seemed to be the answer to our requirements

Apparatus

The installation which we intend to build (fig 1) would allow the X-ray apparatus and the film changer to be switched on by the passage of the mixture of the contrast medium and ^{24}Na at a given level or levels

The film changer would be basically the Royal Northern changer,[2] which will be set to stop at pre-set levels The trigger is a collimated Geiger counter, efficient for the detection of γ-radiation from ^{24}Na The sensitivity depends on the distance of the Geiger counter from the long axis of the limb

There are still a number of technical problems to be solved, the basic idea having been shown to work. Up till now, however, research has been directed to finding the minimum amount of ^{24}Na needed to be an effective trigger, both to ensure against

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[1] *Lancet*, 1958, ii, 1023
[2] Carstairs, L. S *Brit J Radiol* 1960, 33, 526

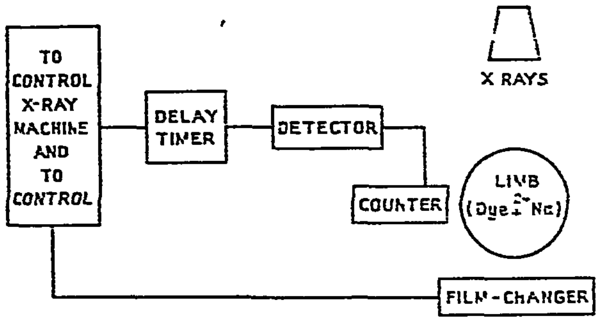

Fig 1—Proposed scheme for "robot" angiography.

raising the background which affects the sensitivity of the apparatus, and to minimise the radiation hazard to patient and staff.

The radiation-detection apparatus consists of a Geiger counter, with slit collimation, connected to a sensitive radiation-measuring circuit provided with a relay which is de-energised when the radiation intensity reaches a certain predetermined level. The response time of the circuit is approximately 0.5 sec. The radiation level at which the relay becomes de-energised may be set over the range of approximately 20 to 200 counts per sec., the break connecting two contacts which operate a light.

Method

In preliminary experiments the ^{24}Na was injected separately before the contrast medium and, in a femoral arteriogram, the time of arrival at, say, the foot was noted. Subsequently, the contrast medium was injected and the film exposed according to the timing previously determined.

In later experiments the ^{24}Na and contrast medium were mixed and the films exposed manually at the time indicated by the flashing light in the detector. This manual method has, of course, the inconvenience of a possible lag in timing. This limitation will be dealt with when full automation is introduced. The "robot" will, however, have a delay timer to allow, when indicated, a selected interval of time to elapse between the stimulation of the counter and the triggering of the X-ray set (fig. 1).

Fig. 2 is an arteriogram of the foot using this method, in which the phase is accurately arterial. The circulation time in this particular patient, who had intermittent claudication and a long block of the femoral artery, was, from the point of injection in the femoral artery just below the inguinal ligament, to the foot 12 sec.

Fig. 3 demonstrates the degree of error possible in peripheral angiography. The film was the last of a series in which we attempted to follow the descent of the dye in the leg by subjective estimation based on clinical data. The result was a film taken about two seconds after the arterial phase, showing well the plantar venous reservoir and a nice saphenous drainage.

The method of arterial injection is percutaneous puncture with a needle of short bevel introduced with the outlet pointing distally. The needle is connected through a polyethylene tube to a syringe, and a saline perfusion is maintained for the duration of the examination.

Once the artery is successfully punctured an assistant prepares a 20 ml. mixture of contrast medium containing 50 μC of a solution of ^{24}Na. This mixture is then injected by manual pressure and as quickly as possible into the artery.

We have observed in the artery a proximal reflux of the bolus of the contrast medium. The length of this reflux depends on the degree and proximity of the arterial block and on other factors, such as blood-pressure and pressure and speed of injection. Nevertheless, this retrograde filling of the artery must have an important effect on the travelling time-table of the contrast medium along the tree, and, on occasions, may mean that injections and exposures have to be repeated, thus subjecting the patient to possible reaction from excess of contrast medium.

Comment

The chief value of this method is to demonstrate the distal arteries in the lower limbs. A number of technical refinements are still required. Perhaps the controversial point is the use of a radioactive substance in order to reduce the amount of radiation involved in arteriography. The radiation dose to a patient at the centre of the trunk per injection of 50 μC of ^{24}Na is of the order of 90 mrad, the gonad dose most probably being less than this. This dose has got to be judged against the following points. The gonad dose with the current arteriographic technique, involving repeated exposures, is of the order of 1500 mrad for 15 exposures[3] in males. Of this dose only about 3 mrad is contributed by each exposure to the lower leg and foot, which are the difficult exposures to time. For the patient, a small gonad dose from X-ray exposures will be saved at the expense of an additional γ-ray dose of the order of 5% of the total X-ray exposure. For the staff, the reduced number of exposures will offer appreciable

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[3] Larsson, L. E. Acta radiol., Stockh. 1958, suppl. 157.

Fig. 2—Radiograph of arterial phase in angiogram of foot using ^{24}Na as time of exposure indicator. Inguinal-ligament/foot circulation time 12 sec.

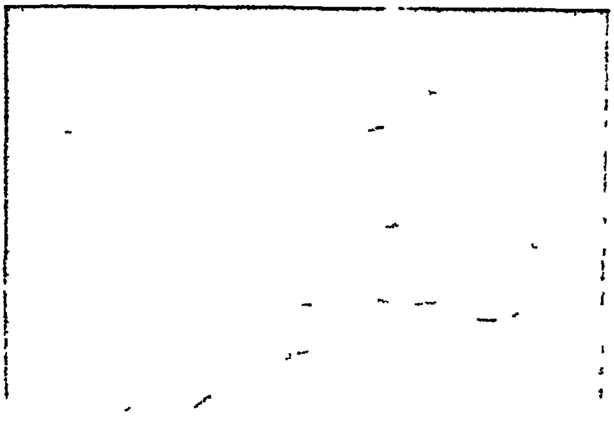

Fig. 3—Angiogram of foot obtained by subjective estimation of circulation time resulting in film being taken about 2 sec. after arterial phase. Only the venous phase is shown.

protection Other considerations are the reduction in examination time and the fact that most patients coming for peripheral arteriography are middle-aged or elderly people for whom a short examination is preferable For the younger patient, too, the method seems justified because it ensures that one injection of contrast medium secures the maximum information

Work is now in hand to find out whether the amount of ^{24}Na can be reduced to a much lower level, which would have the added advantage, particularly when more than one limb is examined, of not raising the patient's background greatly and thus adversely affecting the sensitivity of the apparatus

It is our intention to enlarge the application of the method to other kinds of angiography

We have to thank Dr L S Carstairs for his helpful criticism and Mr Alan Small for referring patients to us We are grateful to Dr K Ashcroft for his aid with the angiographic work, and Sister J Hathway, Staff-Nurse E Cych, and Miss M England were also of much help Miss M Marston gave us patient secretarial assistance We are grateful to Miss V Priestley-Smith, Isotope Developments Ltd, for the initial loan of a Gamma Switch type 656, with which the preliminary experiments were carried out

ADDENDUM

Since this paper was written, recent work on a similar technique has come to our knowledge Greenspan et al[4] have used 50 µC of ^{131}I-labelled renografin detected by a scintillation counter coupled with a ratemeter and recorder This method is essentially the same as ours, but because of the longer half-life of ^{131}I the radiation dose, particularly to the thyroid, will exceed the figures we quoted Gabelova and Frank[5] have also described a technique for studying the peripheral circulation of gamma-emitting isotopes in the body, in particular using 50 µC of ^{24}Na Although this technique is rather elaborate, it seems capable of application to our special problem

Public Health

A Margarine Illness

A NEW brand of margarine is blamed for a widespread outbreak in Holland of an illness whose main feature is urticaria As many as 60,000 people are reported[6] to have been affected The margarine is thought to be associated with 2 recent deaths, and in 1 there is, according to a statement by the chief inspector of the Dutch Ministry of Health, "a serious supposition of connection" between the death and the eating of the margarine[7] Most of those affected are only mildly ill, but a number are in hospital The Ministry of Health is investigating Meanwhile, the manufacturers, Van den Berg and Jurgens, of Rotterdam, a subsidiary of Unilever, have withdrawn all the stock that had been issued, and the old brand of margarine is being supplied instead It is said[8] that the new brand was tested on animals and humans by Unilever for eight months at their research laboratory at Vlaardingen

Cholera in Afghanistan

CHOLERA has appeared for the first time since 1930 in Kandahar, Afghanistan, where 24 cases and 9 deaths were reported in the week ended Aug 20 to W H O by the Ministry of Health in Kabul The first cases were imported from Quetta, West Pakistan, with which Kandahar has direct air communications The Kabul health authorities requested a million doses of cholera vaccine from the W H O Regional Office for South-East Asia, New Delhi

Conferences

SARCOIDOSIS

AN International Conference on Sarcoidosis was held in Washington, D C, on June 1–3, under the auspices of the U S National Research Council and with the support of the National Institutes of Health and the U S Veterans Administration Participants from ten countries described their experiences

DEFINITION OR DESCRIPTION

It is difficult to define a disease of unknown ætiology, protean clinical features, and unpredictable natural history, so the participants instead agreed upon the following description

Sarcoidosis is a systemic granulomatous disease of undetermined ætiology and pathogenesis Mediastinal and peripheral lymph-nodes, lungs, liver, spleen, skin, eyes, phalangeal bones, and parotid glands are most often involved, but other organs or tissues may be affected The Kveim reaction is often positive and the tuberculin test often negative Other important findings are hypercalciuria and increased serum-globulins The characteristic histological appearance of epithelioid tubercles with little or no necrosis is not pathognomonic, tuberculosis, fungal infection, beryllium disease, and local sarcoid-tissue reactions must be excluded The diagnosis should be restricted to patients who have consistent clinical and radiological features together with biopsy evidence of epithelioid tubercles or a positive Kveim test

In an endeavour to ensure international uniformity in recognising and reporting the type of disease, the above description should be qualified by a classification of its acuteness and of its activity, and for this purpose the broad terms subacute or chronic, and active or inactive, with or without functional impairment were accepted Sarcoidosis is defined as subacute if its duration is less than two years from the first objective evidence of the disease, whereas the disease is regarded as chronic if it persists for longer than two years The time-limit set is, of course, arbitrary, but it is hoped that the distinction may serve to segregate transient (or subacute) from persistent (or chronic) sarcoidosis, for the two types differ in their course, natural history, response to treatment, pathology, and prognosis Subacute sarcoidosis is manifested by erythema nodosum, maculopapular eruptions, hilar and peripheral lymphadenopathy, Bell's palsy, and parotitis, it is characterised by a high incidence of spontaneous remission, usually within one year, with few sequelæ, and the prognosis is good Chronic sarcoidosis persists and has a relatively poor prognosis, for the development of pulmonary fibrosis, chronic uveitis, and nephrocalcinosis may be crippling or even fatal

To classify activity of the disease is more difficult, chiefly because there are no precise objective means of establishing inactivity The assessment of activity is largely clinical, and a positive Kveim test may help to support this clinical judgment Inactivity may or may not be associated with functional impairment, such as alveolo-capillary block, secondary glaucoma, or cataract The description of sarcoidosis therefore becomes somewhat more precise if it states whether the disease is active, or, if inactive, whether accompanied by functional disturbances

DIAGNOSTIC CRITERIA

From the above description, it is evident that the diagnosis depends upon a compatible clinical picture

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[4] Greenspan R H Bernstein E F, Loken M K *Amer J Roentgenol* 1960 83 1034

[5] Gabelova N A, Frank G M *Peaceful Uses of Atomic Energy*, 1958, 26 116

[6] *Birmingham Post* Aug 30, 1960

[7] *Times* Aug 29, 1960

(which includes the various radiographic abnormalities) together with histological confirmation obtained either from accessible lesions or blind biopsy techniques or by means of the Kveim test The diagnosis of sarcoidosis is secure and internationally acceptable only when this twofold clinicohistological evidence is demonstrable Just as a clinical diagnosis remains in doubt without histological confirmation, so does a histological diagnosis remain unacceptable without a consistent clinical picture This excludes non-specific local sarcoid-tissue reactions, which are sometimes observed in skin, lymph-nodes, liver, gut, meninges, conjunctiva, or lung in response to trauma, chemicals, infections, and neoplasms

KVEIM TEST

The intradermal injection of human sarcoid tissue may produce a nodule of sarcoid tissue at the site of inoculation in the course of a month in patients with sarcoidosis False-positive reactions are extremely rare, so the Kveim test is regarded as a specific and helpful means of confirming the diagnosis Dr Merrill Chase and his colleagues at the Rockefeller Institute have prepared various fractions and are succeeding in standardising antigens of known and reproducible potency This will lead to increased use of the Kveim test, which has now become an acceptable alternative to other means of histological confirmation

INDICATIONS FOR TREATMENT

It was agreed that corticosteroid therapy was the only method of proven value and that it was particularly indicated for ocular lesions, progressive pulmonary involvement, persistent hypercalciuria, disfiguring skin lesions, and involvement of the heart and central nervous system A minimal course of treatment for subacute sarcoidosis should be of three months' duration at the least dosage likely to suppress the clinical and radiological manifestations In contrast, long-term steroid therapy is necessary for chronic, persistent sarcoidosis

Many participants had noted some amelioration of symptoms and signs following treatment with chloroquine or hydroxychloroquine In a disease with such a high incidence of spontaneous remission, controlled clinical trials are obviously desirable before it is possible to support or refute this observation, and the cases to be included in these trials should be of the chronic, persistent type Dr James G Hirsch and his colleagues are undertaking a pilot trial of this kind at the Rockefeller Institute It was urged that if this yielded promising results, its scope should be enlarged on an international scale

Control trials are also, in fact, sorely needed to evaluate corticosteroid therapy, and plans are being made for these to be conducted at an international level Their necessity became even more obvious when it emerged that the results of corticosteroid treatment in Stockholm (S Lofgren), Philadelphia (M Sones and H Israel), and London (D G James) all showed that treated cases did less well than untreated This apparent paradox in uncontrolled series is probably due to the fact that steroids were withheld until the disease had become chronic and persistent This interpretation underlines our dilemma in choosing the optimum time for corticosteroid therapy It should not be started too early, because of the high incidence of spontaneous improvement, but, on the other hand, it should not be withheld until a late stage of irreversible fibrosis has made the condition irremediable

SARCOIDOSIS IN CHILDHOOD

Only 104 cases of sarcoidosis in childhood had been reported up to February, 1953, since when McGovern and Merritt[1] have added a further 9 examples observed in Washington hospitals In a communication to the conference, Dr Edwin L Kendig reported a further 6 cases seen in the Medical College of Virginia Hospitals, most noteworthy was that 3 of these cases had occurred in siblings—which is unique[2] Of the whole series of 119 children, only a quarter were below the age of 9 years, the remainder being aged 9–15 years, and over a third of the children were Negro Predominant lesions were hilar and peripheral lymphadenopathy and ocular and skin lesions

SARCOIDOSIS IN THE U S ARMY AND NAVY

In 1953–56, 291 cases with clinical and histological evidence of sarcoidosis were observed in U S Army hospitals, these were detected chiefly as the result of routine radiography Colonel Joseph Cooch noted that the incidence was 16 times greater in Negroes than white subjects, and, probably because of this factor, incidence was lower among officers He found no correlation between its incidence and age or length of service, whereas Dr B F Gundelfinger and Dr S A Britten, analysing 303 cases occurring in 1954–58 in the U S Navy and Marine Corps, noted its predilection among enlisted men 20–25 years of age in their second to eighth years of service They found a tenfold higher attack-rate in the Negro race and also observed a higher incidence in white officers than in ratings The time of onset among officers seemed to be about five years later in age or service than that among ratings

WORLD-WIDE EPIDEMIOLOGY

It seems clear that sarcoidosis has a world-wide distribution, although its reported incidence in under-developed countries suggests, perhaps artificially, that it is less often seen there Its clearcut preponderance in the pine-tree belt of the South-Eastern United States is not so evident elsewhere Such a clear-cut association could not be established in their respective countries by Dr Pablo Purriel (Uruguay), Dr Keizo Nobechi (Japan), Dr Ole Horwitz (Denmark), Dr Andrew Douglas (Scotland), Dr G Schonholzer (Switzerland), or Dr B Van Lingen (South Africa) Factors peculiar to their own countries seemed more likely to be at work The higher incidence in North Japan is probably due to the fact that Tokyo and its medical schools contribute to a higher diagnostic standard A heavy incidence of 116 per million population in North Jutland may, in part, have been due to the perspicacity of a physician preparing a postgraduate thesis on sarcoidosis in that area, whereas in Switzerland the incidence was inversely proportional to the rainfall

Dr Stig Wallgren cited a prevalence-rate of 40 per 100,000 in a mass survey of a million Army personnel in Sweden during the past decade, whereas Dr Arthur Robbins has noted a prevalence of about 50 per 100,000 of the civilian population during 1960 in the coloured Harlem area of New York City It is interesting to note the similar prevalence in such different racial populations

ENVIRONMENTAL FACTORS

Foremost among the epidemiologists studying the problem have been Michael[3] and Cummings,[4] whose pioneer work has now culminated in an interesting hypothesis relating sarcoidosis to chemical constituents of pine-pollen This would certainly explain the prevalence of the disease in the pine-forested South-Eastern United States Using pine-pollen antigen as a Mantoux-like skin test, Dr **GEORGE McCUISTON** has surveyed areas of Florida where sarcoidosis is well recognised and common He found positive skin tests in from 5% to 46% of the population in various areas, and made the noteworthy observation that the incidence of positive skin tests was less in patients with sarcoidosis than in controls with other diseases, including tuberculosis This suggests a depression of cutaneous hypersensitivity akin to that noted with other delayed-type skin tests in sarcoidosis In one patient with erythema nodosum due to sarcoidosis in London, pine pollen behaved like Kveim antigen, provoking, in a month, a nodule composed of sarcoid tissue (D G JAMES)

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[1] McGovern, J P, Merritt D M *Advanc Pediat* 1956 8 97
[2] Kendig E L, Jr, Peacock, R. L. *New Engl J Med* 1959, 260 962
[3] Michael M. Jr *Ann intern Med* 1956, 45 151
[4] Cummings, M M, Hudgins, P C. *Amer J med Sci* 1958, 236, 311

Further observations are clearly necessary before deductions can be made concerning the role of pine-pollen allergy, this may be but one of several provocative factors, depending on circumstances and on the area in which the disease is contracted In Georgia, Dr **G W COMSTOCK** has noted that, in Negro females with sarcoidosis, clay-eating is twice as common as it is in matched controls, rural residence was more common, whereas cigarette-smoking was less frequent He felt that the disease had no causal relationship with tuberculosis, but that pregnancy might be a predisposing factor in the community he had studied

Peanut dust is suggested as a possible provocative allergen in Virginia, where Dr **E L KENDIG, Jr**, has noted chronic pulmonary disease among peanut-growers and an unusually high incidence of sarcoidosis among their children

Possibly many factors contribute to the development of sarcoidosis, including constitutional or racial predisposition, and pregnancy or other hormonal states, and to these may be added various regional factors, such as those already cited, which vary with the country and even areas of the country Epidemiological surveys are needed in Britain in an endeavour to detect contributory factors peculiar to this area

MORTALITY-RATES

Dr **I M. MORIYAMA**, of the Office of Vital Statistics, has followed mortality trends in the United States There were 73 deaths in 1949, when figures were first recorded, and they climbed to 196 in 1957 He estimates that the death-rate is about 1 per million population, it is slightly less for the white and correspondingly more for the coloured population

In the series investigated at the Middlesex and Royal Northern Hospitals, there were 15 deaths due to sarcoidosis—13 due to pulmonary fibrosis and cor pulmonale and 2 due to nephrocalcinosis and uræmia (D G JAMES) 12 of the 15 deaths were in women, who seem more prone to chronic skin lesions, and so also to chronic lung lesions The prognosis of sarcoidosis is largely based upon the degree of fibrosis supervening, and the value of corticosteroid therapy will ultimately be assessed on how effectively it prevents these fibrotic sequelæ

The transactions of this conference are to be published by the U S National Research Council

D GERAINT JAMES

In England Now

A Running Commentary by Peripatetic Correspondents

Queen Boadicea with knives on her chariot wheels had nothing on the visitors to our lake this summer They have carved quite a name for themselves with their water-skiing Every Sunday morning the new motorway hurtles a strangely-garbed, and strangely tongued, invasion from the land where the lolly is made one way or another, and spews them out on the shores of our lake Multitone cars with multitone horns, roof racks with crimson water-skis, gleaming speedboats on trailer trollies with tiny smoking bearings, loud check shirts and loud unchecked voices, bikinis and bottled beer We can stand that much with no more than a genteel shudder We can open one eye after lunch and mutter un-Sunday-like things to ourselves *no-one else could possibly hear us over* the scream of the outboard motors and the screams of the popsies awash Jolly good show to see the Nation enjoying their National Park

What fun to scare the daylights out of the silly folk in rowing boats Speedboat to one side, skier to the other, the towline twanging across their defenceless heads, bow wave and outboard wash capsizing them *Bring back the law of the jungle* into the National Park

But we do not begrudge them their exhibitionism it must be almost impossible to rise out of the water without it That was probably how Evolution began in the first place like see no hands on a bicycle like see no eyes at the wheel of a speedboat Much more fun to let instinct take control, to gaze at Venus leaping from the waves at twenty knots than to keep a puritanical eye on the sterile fission of the water ahead If the swimmers and the stupid squares in rowing-boats and sailing dinghies cannot nip out of the way of a roaring spray *plumed speedboat*, it serves them right if they get run down They must have had warning enough, and if they are not prepared to keep up with the pace of modern life they should get to hell out of it *Progress rides roughshod over back-markers*

Boadicea's chariot wheels never touched the r p m of an outboard her knives were not in the same class as a screaming propeller We have fished out one mastectomy, one laminectomy of the dorsal vertebræ with extirpation of the scapula, and one young boy with the top of his skull sliced open Even the Iceni would have claimed *that* as a *Roman holiday*. Perhaps Boadicea had twinges of remorse herself

• • •

It seems to be an English custom to compliment the foreigner on matters which in this country would be cause *for complaint* Take for instance the rapid repair of the storm damage on the road near Brienz described by my peripatetic colleague So far as I can gather this is a regular occurrence *Last year I had the same experience*, and when I arrived three hours late at my hotel in Interlaken the manager said this was nothing new and that the obstruction often delayed travellers longer than it did me Yet the railway *line running* alongside the road is rarely damaged because it has been built on solid stone piers I imagine that the movable bridge is kept conveniently round the corner and that the workmen are permanently *on call*, including, in my case, a bulldozer Would this state of affairs be tolerated in England without the usual grouse, and would a foreigner pat us on the back and say how wonderful for us to repair so quickly *a road* which is so regularly washed away ?

• • •

Since my wife has been lured from general practice into matrimony, her supply of clinical *material has* been limited But the change has given her enough time in the home to observe that her mother's bronchitis was due to allergy to flour and to alter the kitchen routines to eliminate every trace of *flour from* cooking techniques It has also given me a public reputation for ruthlessness in geriatric work which is reinforced every time we take the family into a *café for* tea "A tray of tea, please Toast and cakes for four and a packet of crisps for the old lady "

• • •

When Universal Detergents found that the large-scale production of their immensely popular Shrift (shortens every washing day or washing-up) had landed them with an overwhelming quantity of xo 7, an apparently worthless by-product, they were really up against it The trouble was that xo 7 could not be incinerated, unloaded into the public sewers, or even dumped into the sea without causing an abominable stink. The U D board of directors were at their wits' end to find an outlet for the stuff before it engulfed the whole outfit including themselves Rapidly they mobilised all the pharmacological boffins who were slaving away with their pharmaceutical subsidiaries, hastily diverted them from the concoction of alternative antibiotics, phenothiazine analogues, super-anabolic steroids, or what have you, and turned them full blast on to the disposal of xo 7

The psychopharms were the first to report with the rush-release of a most exciting film showing that xo 7 made their Japanese fighting fish not merely indifferent to one another but ready to shake fins and play the most wanton games of tag around the tank. Here, in fact, was the ultimate tranquilliser, one that might mend broken marriages or even bring the Cold War to an end. But before the board could settle the advertising allocation, the antibiotic unit excitedly announced that xo 7 had an all-embracing antimicrobial spectrum, ranging the whole way from the viruses to the rickettsiæ The obvious trade-name they suggested would be Vibgyormycin The board now had a tough decision on their table—whether and how to put across the first, and surely it must be the only, tranquillising antibiotic

Before they had made up their mind at least a month had gone by and the stately steroid circus (three-ring) paraded their confident declaration that a single non-toxic dose of xo 7 by mouth completely suppressed mammalian ovulation for, literally, an indefinite period Now the board began to stir uneasily It was true that here might be their salvation from that ever-threatening take-over bid What could be better than a contraceptive with which to fight the fertiliser tycoons But xo 7, though synthetic, was a simple substance and patenting could hardly protect it. Wrongly handled, there was a risk that it might knock the bottom out of the entire drug industry The nation's drug bill might be halved overnight and then rapidly reduced to negligible proportions The whole thing was manifestly impossible Another way out must be found

And then someone noticed the grass round the menacing mounds of xo 7 It was superb, a green-keeper's dream—not a dock, not a dandelion, to be seen Here, thank goodness, was the answer Science, with a capital S, in the service of the sweating do-it-yourself home gardener There is, after all, a lot of lawn in this rain-sodden country Spread out over it in well-diluted form xo 7 does not smell any worse than its parent substance in our kitchens, but the inner history of Sward, the new and very successful selective lawn weedkiller, remains a closely guarded secret

* * *

Christopher, aged six, suffered from recurrent boils, so when I called to visit his younger sister, I thought it wise to test his urine. I gave him a bottle and asked for a specimen of water A few moments later a worried face appeared round the bedroom door "Do you want it from the hot tap or the cold?"

• • •

THE BIOCHEMIST

I am the very model of a modern medicine fitment.
For forward-looking hospitals, essential equipment
On paper or by telephone or discussions over lunches,
I provide the facts and figures to substantiate your hunches
In a matter of a minute I supply the diagnosis,
I'm the crystal ball's successor in all problems of prognosis
I assist in patient planning, I assess the daily treatment
I am the very model of a modern medicine fitment.

(With apologies to a recent advertisement for an electronic brain.)

Letters to the Editor

INJURY AND ABSENTEEISM IN SMOKERS

SIR,—No-one who has had the disconcerting experience of motoring behind a driver lighting-up at the wheel, or had his petrol tank filled by a smoking attendant, or seen the gas mains being repaired by a cigarette-handling engineer, or heard of miners who smoke at the pit face, or witnessed a patient with cor pulmonale trying to light a cigarette in an oxygen tent, will find the greater liability to injury in young smokers as surprising as your annotation of Aug 6 suggests

Nor would such an observer have recourse to theories that these young men must have "impaired muscular coordination" or be "constitutionally accident-prone" The more likely explanation would be a simple mechanical one for the manipulative ritual involved in lighting a cigarette, particularly under adverse conditions, precludes normal accuracy in the simultaneous performance of other "skills" Admittedly, such light-handedness can develop remarkably with practice and permit smoking to be synchronised with such varied activities as infant feeding, ambulance driving, food-handling, or hair-dressing But the safety margin under the more exacting conditions of industry must often be dangerously reduced, and the consequent accident-proneness is surely inherent in the activity rather than inherited by the individual

A time-and-motion study comparing the industrial performances of smokers and non-smokers should now be initiated. The purchasing, lighting, smoking, and disposal of cigarettes is a time-consuming business, and the indulgence in, say, one packet per shift must waste a significant proportion of the working time.

The carefully fostered myth that cigarette smoking increases physical and mental efficiency must be rejected once and for all, and the medical and social reasons for this condemnation should be widely publicised

Manchester J P ANDERSON

SIR,—Your annotation seems to associate the evidence for the carcinogenic effect of cigarette-tobacco smoke on the respiratory system with the effect on accident-rate and absenteeism of cigarette smoking Surely the association is merely verbal depending on the word "cigarette" The painstaking "research" on 3341 men would have been as unrevealing and as futile if, say, general fidgetiness, tea drinking, or dancing had been considered in relation to accident proneness

Hove. G M WAUCHOPE

MALIGNANT MALARIA AFTER BLOOD-TRANSFUSION

SIR,—In their interesting report in your issue of Aug 27 Dr Grant and his colleagues say "In 1936 Thomas et al described the first case in Britain" This may be true if the statement is applied to transfusion of blood for its therapeutic effect, but it may give a wrong impression if it is applied to intravenous infusions in which blood of another person may be accidentally admitted to a patient's circulation and if Ireland in 1917 may be included with Britain Any discussion on accidental infection with malaria through intravenous infusion should not omit mention of 11 cases of malignant tertian malaria which occurred at the Military Hospital, Portobello Barracks, Dublin, between Nov 21 and Dec 28, 1917, and were attributed to the passage of blood from some carrier through the medium of the infusion apparatus then used for the intravenous administration of "606"

Of the 11 cases, 9 proved fatal, and the diagnosis was proved by Prof A C O'Sullivan's very complete examination of necropsy material from 6 of the cases Details of the occurrence were given in the second report of the Salversan Committee of the Medical Research Council (*Special Report Series* no 66, pp 56–60) As evidence of the smallness of the amount of blood which can convey infection, the Salvarsan Committee said inter alia " It is stated that two or three drops of blood containing summer-autumn parasites injected subcutaneously can produce an experimental infection " From an experiment which I made when I was assisting in the investigation of the Portobello cases I concluded that even less than this amount should suffice For the information of readers who have never seen 606 given, it should be explained that the dose was contained in about 250 ml liquid and reached the needle from an infusion funnel via a rubber tube into the last two or three inches of which had been inserted a short piece of glass tubing This was for verification of the needle's entry into the vein, for blood was first allowed to flow back into the glass tube After this the dose of 606 was allowed to flow into the vein and was followed by about 50 ml saline to clear the needle of the drug The unanimous view of the committee, of which I was a member, was that remnants of a carrier's blood left after all that liquid had flowed through the tubing had been swept into the next patient's vein It seemed incredible that any could have remained, considering how very small was the amount of blood allowed to flow back to the inspection window before starting the inflow of 606, and I made the following severe experiment I filled the last four inches of tubing and needle with blood and then allowed 240 ml saline to flow through tubing and needle before collecting 10 ml in a centrifuge tube This amount I spun out for several minutes and then counted the cells in the deposit There were, as far as I can remember, not more than 140,000 cells in that 10 ml after 240 ml had flowed through the tubing

London, S W 1 L W HARRISON

CORTICOTROPHIN AND LONG-CONTINUED STEROID THERAPY

SIR,—Dr Walkden (Aug 6), very properly concerned by the dangers of adrenal cortical failure during steroid therapy, suggests that corticotrophin should be made available to general practitioners The suggestion is a most reasonable one even if it were based solely on a claim that corticotrophin is still used on occasion for treatment and for maintenance therapy A question of some importance arises, however, with regard to its value when used to prevent possible collapse from adrenal cortical failure It seems that there is little evidence that injections of corticotrophin given at intervals during oral steroid treatment will in fact protect against adrenal failure in times of stress

Young and his colleagues [1] reported that 100 mg of adrenocorticotrophic hormone (A C T H gel) weekly failed to maintain normal adrenal responsiveness during corticosteroid treatment and that 200–300 mg weekly was not always effective Dewar and Whyte [2] investigated three patients who had received concurrent treatment with corticotrophin during maintenance therapy with prednisolone and found that only one showed a satisfactory adrenal cortical response to a stimulation test. Controlled investigations in a much larger number of cases are required to solve the clinical and therapeutic problems set by long-term and also by short-term steroid therapy but the complexities of adrenal physiology and the difficulties of present techniques raise a barrier

On theoretical grounds alone, there seems to be little justification for the use of corticotrophin as a " booster " during prolonged oral steroid therapy Even if it did stimulate the atrophic adrenal cortex, corticotrophin would thereby further inhibit the pituitary and thus aggravate the interference with the pituitary-adrenal function which is the real factor of importance in any response to stress Physiological reaction to stress is not mediated directly by the adrenal cortex acting alone, the pathway is indirect by way of the higher levels of cerebral cortex, hypothalamus, and pituitary For this reason prolonged treatment with corticotrophin itself is not without danger, and collapse during surgery may occur in patients who are receiving such therapy

Glasgow W A DEWAR.

SHORTAGE OF RADIOGRAPHERS

SIR,—As a science teacher who actually heard one of the lectures given during Dr Osborne's radiographer recruitment experiment, I can confirm that it aroused great interest among the girls They were particularly fascinated by the slides Schoolgirls are much more interested in lectures associated with slides or a film than in lectures without either

A great deal of the success of the lecture was due to the fact that the lecturer was young enough for the girls to be able to identify themselves with her, and to ask her questions freely

Any girl who has the ability to pass five G C E subjects and who stays at school until she is eighteen will probably by then look to a more academic career than radiography More recruits would be attracted if training started at seventeen

London, W 2 CLAIRE MADIGAN

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—Dr Carter's letter of Aug 13 contained much excellent practical advice on how a diabetic can successfully maintain a syringe sterile with the minimum amount of trouble, but I disagree with his advising storage in surgical spirit

Surgical spirit (*B P C*) is available in two forms, and is adulterated with either castor-oil, methyl salicylate, and ethyl phthalate, or with castor-oil, mineral naphtha, and ethyl phthalate For this reason I think 70% industrial spirit is a far more suitable solution for keeping syringes in I suspect that the reason why surgical spirit was originally advised is that it is the only spirit solution which can be purchased without a doctor's prescription

The Radcliffe Infirmary, Oxford B J CUDDIGAN

SIR,—Dr Stephen Carter's letter was very interesting

I have been on daily doses of insulin since August, 1923, and as my work entails regular visits to hospitals throughout the North-West on business, and I am away from home for several days at a time, I normally carried my insulin syringe with needle in situ, in a spirit-proof case filled with industrial methylated spirit I carried some 1 oz bottles of sterile water with me, so that I could remove all the spirit from the syringe and needle, before loading with the required dose of insulin

Normally a needle would last me two to three weeks—but during the past ten years of injecting, I found that the needles blunted more readily because fibrous tissue was developing at the sites of injection, and they had to be changed more frequently I made a practice of boiling the syringe, needle, and case once a month

Dr Carter does not reassure me as to the efficiency of his method of loading his syringe I am convinced that before this can be done satisfactorily the plunger of the syringe should be raised to the mark on the barrel corresponding to the required dosage, and then the needle plunged through the rubber cap of the inverted bottle, the needle point being below the surface of the insulin The air from the syringe is then injected, making it possible to withdraw the insulin without difficulty Withdrawals of insulin from the bottle should only be carried out with sterile needle and syringe With Dr Carter's method there is a risk of contamination

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[1] Young, I I, De Filippis, V, Meyer, F L, Wolfson, W Q *Arch intern Med* 1957, 100 1

[2] Dewar, W A, Whyte W G *Brit J Derm* 1960, 72, 31

No doubt pathologists would view with horror some of the methods employed, although we diabetics seem to get away with it and keep on living

No doubt also I will shock Dr Carter's sense of economy when I point out that for the past five months I have used only the 2 ml sterile disposable plastic syringes and needles After using it once, I decapitate the needle shaft from its mount and place it carefully in an ash-tray, the separated syringe and barrel are then popped into the wastepaper basket, and I now get my extra twenty minutes in bed too

Poynton, Stockport,
Cheshire

R MERRYWEATHER SHAW

PENICILLIN "B"

SIR,—Dr Fairbrother and Dr Taylor (Aug 20) disagree with some findings and conclusions of my own May I say that I find their argument illogical? They begin by casting doubts on the higher blood levels obtainable with penicillin "B" ('Broxil') than with penicillin V, and then report findings of their own which confirm that these higher levels are attained They appear to contest my finding that lower concentrations of penicillin B (and V) than of G inhibit the growth of staphylococci of intermediate degrees of resistance, and then present results with such organisms in which B is shown to be more active than G by differences of up to 8-, 16-, and 64-fold according to the size of the inoculum

It seems to me perfectly reasonable to conclude that penicillin B, with its much lesser susceptibility to destruction by staphylococcal penicillinase, is more likely to be effective than penicillin G in an infection by a staphylococcus forming this enzyme Dr Fairbrother and Dr Taylor appear to take the view that penicillin in any form is useless in such an infection if this is their belief they should recognise that not everyone shares it The recent discovery of a new penicillin unaffected by penicillinase is not the whole answer to this problem, because domiciliary treatment with this new penicillin will be impracticable

Department of Pathology,
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LAWRENCE P GARROD

OUR POOR THAMES

SIR,—I was interested to read the letter of Dr Longmore and Dr Thompson (Aug 20) on the pollution of the Thames In November, 1957, a survey of the bacteriological standard of natural water-supplies in the vicinity of Reading was undertaken by myself and my fellow undergraduates

Specimens were collected under standardised conditions, as suggested in the Ministry of Health report on *The Bacteriological Examination of Water Supplies* (1956), and were examined within two hours of collection The weather at that time was fairly good and no rain had fallen during the days preceding the examination

The results are shown in the accompanying table These may serve to confirm the findings published previously and indicate that serious pollution of the Thames occurs much further upstream than is assumed by your contributors

I wish to thank my former colleagues for permission to publish their results

St. Helier Hospital,
Carshalton

BASIL JARVIS

INFECTIOUS AIRBORNE PARTICLES

SIR,—In the interesting paper by Professor Rubbo and his colleagues (Aug 20) there are several things which invite comment They discuss the importance of particles which "remain airborne" on the basis of settle-plate counts They conclude that droplet nuclei "play a minor part in contaminating a ward environment" and that their findings "are consistent with the concept that airborne infection in hospital wards is caused by the dispersion of pathogens travelling either as free organisms or in association with the microscopic fibre particles which we have termed fibre nuclei"

While the first of these conclusions is true and the second may ultimately prove to be true of certain infections, neither can be established by the methods employed

As Wells[1] has shown, there are essentially two families of infectious airborne particles (1) those, like droplet nuclei, which are so light that they do not settle in the gently moving air of occupied places and are removed by ventilation, (2) those which settle before they are removed by ventilation and consequently accumulate on horizontal surfaces including settle-plates

This distinction, as Wells has tried to make clear in his book, has a number of important consequences In the first place, particles which do not settle do not contribute to residual environmental contamination and cannot be collected on settle-plates The particles, including "fibre nuclei", which Professor Rubbo and his colleagues have collected on settle-plates, therefore, cannot belong to this group and droplet nuclei cannot have the "same dispersability as fibre nuclei" It is also likely that any "free organisms" present in the air would behave like droplet nuclei

Secondly, the number of particles in the air is not, in itself, a measure of their hygienic significance Droplet nuclei, for example, reach the host by inhalation and because of the very large volumes of air sampled in the course of normal breathing, concentrations of these particles of one in several thousand cubic feet of air may be hygienically significant[2] Since airborne organisms, like any other, can produce disease only by reaching the susceptible tissues of the host, unless the

BACTERIOLOGICAL CONTENT OF NATURAL WATER-SUPPLIES IN THE VICINITY OF READING

Specimen	Colony count per ml on nutrient agar		Ratio of counts	Presumptive coliforms per 100 ml MacConkey bile-salt broth		Presumptive *Strep fæcalis* per 100 ml.	*Cl welchii* count per 100 ml
	22°C/4 days	37 C/2 days	22 37	37°C/48 hr	44°C/48 hr	Glucose azide broth 45 C/48 hr	Wilson & Blair agar 37 C/48 hr
River Kennet upstream of Reading	750	1620	1 2	>1800	Not done	>1800	<5
River Kennet downstream of brewery in Reading	110,500	7500	3 1	>1800	>1800	1300	<5
River Kennet in lock downstream of of Reading	Not done	Not done		>1800	>1800	550	5
River Thames at University Sailing Club	25,000	4400	5 5 1	>1800	>1800	215	50
Clay pit at Sonning-on-Thames	6780 4049	2027 1376	3 1 3 1	900 250	170 45	17 50	<5 <5

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[1] Wells W F Airborne Contagion and Air Hygiene. Cambridge, Mass 1955

[2] Riley, R. L, Mills, C. C., Nyka, W, Weinstock N, Storey, P B, Sultan, L U, Riley, M C, Wells, W F *Amer J Hyg* 1959, 70, 185

superiority in this respect of a given particle can be demonstrated, its numerical superiority in the air is of doubtful significance

In attempting to relate airborne particles to infection, the relative numbers of particles such as droplet nuclei and fabric fibres cannot be established without volume sampling methods which sort particles into groups according to whether they settle or not Even with this information available, the hygienic significance of any group of particles cannot be established without demonstrating a correlation between the presence (and removal) of the particles and the presence (and control) of the infection which they supposedly transmit

Bland-Sutton Institute of Pathology,
Middlesex Hospital,
London, W 1 FRANCIS O'GRADY

OBSTETRIC FLYING-SQUADS

SIR,—I am disappointed that, in your annotation of July 30, you should fail to understand the purpose of the obstetric flying-squad in this day and age

First, it has a very limited value in the resuscitation of the moribund This job must be done by the general practitioner He has the equipment, dried plasma, and giving sets He has the skill—he has been trained in an obstetric unit He is probably at the confinement, but if not he has been notified that his patient is in labour and he has contracted to be available should the midwife need him Naturally he may need further help and advice He calls up his reserves—that is, the hospital There are two alternatives Either he sends the patient to hospital or he calls the hospital to the patient This, then, is the purpose of the flying-squad Certainly the general practitioner will want help quickly, but it is not in a matter of minutes I believe you are wrong to say that delay of half an hour or an hour in the arrival of blood may mean death to the mother Blood-transfusion experts are chary of giving blood that is not cross-matched between donor and patient Cross-matching takes two hours in the laboratory The patient may need blood eventually, but she will survive on a plasma transfusion even if her hæmoglobin is temporarily only 50%

Once the idea of bringing the hospital to the patient has been established, an idea which was considered valuable in the late war, it will help both general practitioner and his patient For instance, the general practitioner may feel that he needs assistance with a persistent posterior and the patient will feel that she has the expert attention of a hospital without all the worry of an emergency admission

Plan as carefully as you like, you will still not do away with emergencies in domiciliary obstetrics Again there are two alternatives Either develop the flying-squad in such a way as to give confidence to general practitioner and to the mother, or deliver all mothers in hospital

Cambridge CLEMENT W WALKER

*** In the management of shock due to serious hæmorrhage it seems dangerous to regard plasma as an alternative to blood blood is needed and the quicker it is given the better Delay in the arrival of the flying-squad can indeed be fatal, and this point is emphasised in the recent report[1] on maternal deaths Regional blood-transfusion officers rightly advise against the routine transfusion of blood which has not been carefully cross-matched But the circumstances of a flying-squad call are exceptional and a calculated risk is justified In certain centres where there is considerable demand on the flying-squad, the blood set aside for the service is specially double-checked to ensure that it is group-O rhesus-negative, and it is also screened for anti-A and anti-B hæmolysins Persistent occipitoposterior position of the vertex is hardly a complication of labour to be managed, by choice, in the patient's home Delivery may well be difficult and is better carried out in hospital While we applaud t contribution made by the emergency obstetric service t the reduction of maternal mortality, we still believe th careful examination of the circumstances of each ca would lead to a fuller understanding of the true place o the flying-squad in obstetric practice —ED L

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[1] Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1955-57 H.M Stationery Office, 1960

REGIONAL PLAN FOR ACCIDENTS

SIR,—Being merely a doctor, I cannot see wh accidents should not be treated in the local hospita Surely with every accident we have to obey the Ecclesi astical instruction "Make no haste in time of trouble I have seen and read in the Press of many deaths wh have occurred when this rule has been neglected, and have given accounts of patients who have survived a made excellent recoveries when they were treated priman in the home and local hospital[1] Such patients escap the marvellously skilful operations—and profited

Edgbaston, Birmingham JAMES F BRAILSFORD

HYDROCORTISONE BY INHALATION

SIR,—We were much interested in the paper of D Langlands and Dr McNeill (Aug 20) on a trial of hydr cortisone inhalation in asthma We have carried out similar trial in asthmatic children, measuring the resul in terms of the forced expiratory volume in one seco (F E V $_{1\,0}$)

14 children were allocated by random selection to two grou The first was given hydrocortisone by inhalation for ten wee followed by a placebo for ten weeks The second group start with the placebo and continued with the hydrocortisone in t same ten-week periods Hydrocortisone acetate was deliver from 'Medihalers' as a micronised powder, and the placeb consisted of medihalers identical in appearance, but containi propellant only Each patient was instructed to take six pu daily, equivalent to a total dose of 9 0 mg of hydrocortison

The results of F E V $_{1\,0}$ converted to a percentage of the mea normal value for the child's height[2] are shown in the accom panying table The results in period 2 were better than i period 1 by 3 8% of normal and the results with hydrocortison were better than with the placebo by 3 4%

Analysis of variance showed that neither of these change was statistically significant An apparent interaction betwee

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1 J internat Coll Surg August, 1960
2 Strang, L B Thorax, 1959, 14, 305

F E V $_{1\,0}$ READINGS EXPRESSED AS PERCENTAGE OF NORMAL FOR HEIGH

Case no	Sex	First period						Second period					
		Hydrocortisone					Means	Placebo					Means
2	M	22	30	54	29	36	34 2	42	61	61	29		48 2
4	F	44	74	56	71	69	62 8	61	63	83	71		69 5
6	F	31	48	37	34	22	34 4	34	24	37	37	31	32 6
8	M	61	71	74	63	35	61 8	60	70	75	68		68 2
10	M	85	88	77	67		79 2	61	71	82	82		74 0
12	F	75	80	80	80	89	80 8	77	53	86	49		66 0
14	F	35	39	48	58		45 0	31	67	64			53 5
16	M	70	101	102	104	97	94 8	69	100	36	96		75 2
Totals for order group 1							61 6						63 3
		Placebo					Means	Hydrocortisone					Means
1	M	75	98	79	87		84 8	78	88	89	93		87 0
3	M	41	80	87	92	111	82 2	91	114	108			103 3
5	M	112	118	113	110	110	112 6	107	118	116	120		115 2
7	M	65	67	62	68	64	65 2	80	79				79 5
9	M	30	55	34	47	61	45 4	44	69	82	45		60 0
11	F	38	38	68	78	81	60 6	80	71	65	90	71	75 4
Totals for order group 2							74 8						86 3
Totals for both order groups		Period 1					67 1	Period 2					70 9
		Hydrocortisone					70 6	Placebo					67 2

"treatment" and "order" gave us some difficulty in interpretation since the experimental design confounds "order" with "children" However, we felt that we could safely say that the benefit attributable to the drug, if it existed at all, was only of the order of 3% of normal and not more than 7 5% of normal and that there was no real evidence that different children reacted very differently to its administration We regard this last aspect as important in any drug trial, because a marked variation in response of individuals to a drug will not be apparent from a consideration of the mean results alone

These findings in a different age-group confirm those of Dr Langlands and Dr McNeill and draw attention again to the need for objective measurement in assessing the results of treatment in asthma

We are grateful to Messrs Riker, Loughborough, for the supply of medihalers containing hydrocortisone acetate and for the placebo medihalers

Department of Child Health,
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University of Durham

L B STRANG*
E G KNOX

ELECTROCARDIOGRAPHIC CHANGES DURING ANÆSTHESIA

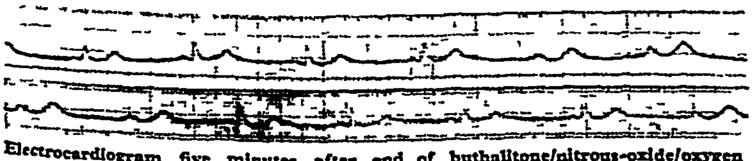
SIR,—I was most interested in Dr Zuck's letter of Aug 20 about his two cases with abnormal electrocardiograms, because I have seen a similar case myself

This arose in a man of 55, in the course of a recent investigation into the action of thiobarbiturates on the electrocardiogram[1] There was no history or clinical signs of cardiac disease and the pre-anæsthetic control electrocardiogram of the standard and augmented limb leads showed no abnormality The patient had undergone cystoscopy under buthalitone/nitrous-oxide/oxygen anæsthesia and the accompanying record was taken five minutes after the anæsthesia had been discontinued.

The tracing (lead II) shows the P wave becoming fused with and distorting the QRS, reverting to its original position and then returning to the QRS As in Dr Zuck's two tracings, the RR intervals are constant while the PR, RP, and PP intervals are variable

Almost every known form of cardiac arrhythmia has been reported during trichlorethylene anæsthesia,[2] and nodal rhythm often arises under any type of anæsthesia and is considered to be of little clinical significance[3] Dr Zuck has suggested that the effect may be due to the almost synchronous discharge of impulses arising in the sinoauricular and atrioventricular nodes with the former suppressing the latter Such a mechanism has been described[4] and a very similar picture is produced This type of arrhythmia, however, is associated with sinus bradycardia and the PP intervals are constant Neither of these features are present in Dr Zuck's or my electrocardiograms

It seems most likely that these three cases are examples of a relatively uncommon but recognised type of phenomenon known as a wandering pacemaker or shifting or sliding nodal rhythm While some cardiologists consider that this condition is due to the site of stimulus formation continually moving across the atrial muscle between the S A and A V nodes,[5] others consider it to be a nodal rhythm with variations in the rate of conduction of impulses back to the atria[6] The effect is the production of a fairly constant RR interval with variable PR, RP, and PP intervals and these changes may be seen in all three tracings



Electrocardiogram five minutes after end of buthalitone/nitrous-oxide/oxygen anæsthesia. There is an interval of approximately 2 1 sec. between the upper and lower tracings

Ryde,
Isle of Wight.

J MACKETT

SIR,—The basic mechanism involved in the disturbance of cardiac rhythm during anæsthesia with trichlorethylene, noted by Dr Zuck, seems to depend on the existence of a homogenetic idioventricular ectopic pacemaker situated above the bifurcation of the main bundle of His, and probably below the atrioventricular node Retrograde conduction from this centre is blocked, so that the atria continue to be activated by the sinus node

It may be that the sinus impulse passes theough the atrioventricular conducting tissues for some way before it is blocked, thus rendering them refractory for the retrograde impulse from the ectopic centre—i e, the retrograde ventriculo-atrial block has a physiological and not a pathological explanation, and does not depend upon organic disease in the main bundle of His Hence two pacemakers exist in the heart side by side competing for the conducting pathways in the presence of normal atrioventricular conduction—i e, a pararrhythmia is present, with sometimes nodal and sometimes sinus rhythm As the two centres have almost identical frequencies the P waves and QRS complexes have a close relationship in time This explains the "emerging" P waves, and a type of reversed Wenckebach phenomenon Vagal hypertonia may be an important factor in this disturbance of rhythm

Belfast City Hospital.

E FLETCHER

BACK PAIN AND HYPERÆSTHESIA

SIR,—To sum up the letters you have published on this subject, their authors fall into two groups as might have been expected on the one hand the qualified men who practise unashamedly osteopathic techniques, and, on the other, qualified men whose manipulation is justified in terms of classical anatomy of the intervertebral disc and its effects on the nerve-roots of the central nervous system

The fact that both groups feel that my paper is an important contribution demonstrates that although manipulation is successful, we are still very ignorant, in my opinion, as to why it is

We must clear our minds completely of previous theory and investigate this commonplace condition with every modern technique that is available Ordinary still X-ray films have shown nothing, perhaps high-speed slow-motion X-ray studies of the spine during manipulation would be fruitful, or perhaps electrophonographic studies of the "click", or finally the detailed postmortem dissection of the segment of the spine at fault in patients known to have had a recurrent syndrome or an acute attack immediately before death.

In all these investigations each patient must satisfy all four points of the syndrome, namely (1) dull ache, (2) limitation of a spinal movement by pain, (3) paravertebral tender spot, and (4) its overlying area of hyperæsthesia

This syndrome will not only be useful in ensuring that all investigators are studying the same condition, but will also ensure that they are investigating the correct vertebral level and correct side of the trunk in each case

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* Now at Hammersmith Hospital, Ducane Road, London, W 12

1 Henderson, A. G, Mackett, J, Masheter, H C. *Brit J Anæsth* 1958, 30 302

2. Wylie, W D, Churchill-Davidson, H C. A Practice of Anæsthesia, p 197 London, 1960

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5 Goldberger, E. Unipolar Lead Electrocardiography and Vectorcardiography, p 375 London, 1954

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Medical Department,
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Chippenham, Wilts
JOHN R GLOVER

DOCTORS, ADMINISTRATORS, AND THERAPEUTIC COMMUNITIES

SIR,—Dr Crocket's article (Aug 13) deserves close attention and is a challenge to some long-overdue rethinking on this subject

His concept of the division of medical administration into three categories—clinical administration, supportive administration, and administrative therapy—may at first appear difficult to assimilate, but it seems that the key to each category is the qualifying adjective

I should like to comment on Dr Clark's appreciative letter of Aug 27 Dr Clark has difficulty in conceding validity to the separateness of the concepts "clinical administration" and "administrative therapy" May I use the example he quotes to point out the distinction as it occurs to me?

Dr Clark asks "When a consultant psychiatrist holds a ward staff meeting and discusses with the ward doctor, the sister, and the nurses the attitudes they are to adopt towards an individual patient, is this 'clinical administration' or 'administrative therapy'?" It might be said to be both in so far as the wording of the proposition appears to indicate two opposing ideas, or appears to me to do so "Discusses" implies participation and the supportive role, but "the attitudes they are to adopt" seems to imply, consciously or unconsciously, an authoritarian attitude, and therefore presents a characteristic of administrative therapy

The example given by Dr Clark appears to raise a further question Is it part of a consultant's role to hold ward staff meetings unless he is directly in charge of the ward? Surely the ward doctor should be "holding" the meeting The consultant's role is rather to facilitate these meetings If he does participate, he should be prepared to surrender his accustomed leadership role to the actual leader in the situation, the doctor in immediate contact with the patients of the ward It is surely no part of a consultant's role, except in rare circumstances, to try and control—i e, administer—therapeutic situations, but to try and understand their needs and to facilitate the expression of these needs

Dr Clark's contribution is to be welcomed, and it is to be hoped that it will stimulate others to think about this problem and contribute to its solution

Shenley Hospital,
near St Albans
B C GILSENAN

SMELL OF "ACETONE"

SIR,—Absence on holiday has prevented me until now from commenting on the letter from Dr Baker (Aug 13) on this subject When I wrote acetone I meant "acetone" and it would have been better if I had said "ketone bodies" or some such phrase I doubt whether the incidence of non-smellers is as high as 50%, however, but there has apparently never been a survey There is some analogy, perhaps, with inability to taste phenylthiocarbamide, an odd taste defect which has been thoroughly investigated It is due to a recessive gene and about 25% of our population are non-tasters My colleague Dr J Fraser Roberts has drawn my attention to another curious smell defect which is, for obvious reasons, not easy or safe to test as it concerns the ability to smell hydrocyanic acid However, Kirk and Stenhouse[1] have shown that 18% of white Australian males are unable to smell solutions of potassium cyanide and the defect behaves almost but not completely as a recessive sex-linked character Allison[2] found 25% of non-smellers among males of the Luo and Kikuyu tribes in Kenya I am indebted to Dr Fraser Roberts for this detailed information

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ALAN MONCRIEFF

RELIEF OF PAIN IN RESPIRATORY FAILURE

SIR,—In your issue of Aug 27 Dr Judge and his colleagues quote me as having found that the administration of pethidine produces an *in*crease in the respiratory rate I presume that there has been an error, what I (and others) have reported is, of course, that pethidine causes a slowing of the respiratory-rate and a diminution in pulmonary ventilation

Incidentally, it has been shown by Mastio and Allbritten,[3] that in the presence of postoperative pain injection of pethidine will produce an increase in ventilation, similar findings were reported by Curreri et al[4] employing levorphanol ('Dromoran')

Dr Semple (July 23) proffers evidence that the administration of a narcotic antagonist together with a narcotic does not entirely abolish the respiratory depressant action of the analgesic While this may be true, I believe it has been clearly established[5-9] that the mixture of an antagonist with a narcotic considerably diminishes the respiratory depressant effect of the analgesic drug

Manchester
MARK SWERDLOW

HOSTEL NEEDS FOR BACKWARD CITIZENS

SIR,—It is unfortunate that Dr Stein and Dr Susser, in their otherwise careful and useful review last week of the social progress of former pupils at schools for the educationally subnormal, fall into the prevalent error of making sweeping statements about the past disposal of subnormals which are not borne out by their own statistics

At the outset of their paper they state "The legislation of the past half-century has led to the confinement of many of the mentally subnormal in large institutions" Their own statistics *in fact show that out of a total of 106 educationally* subnormal pupils, now aged 20–24 years, a total of 9 had been admitted to institutions—8 to mental deficiency hospitals and 1 to a mental hospital Of these, 7 have been returned to the community, and 1, having absconded, has also returned to the community and is presumably independent, leaving only 1 still in hospital The average length of stay seems to have been five years

An admission-rate of 8·5% does not appear to justify the use of the term "*the confinement of many of the mentally subnormal* in large institutions" It is clear too that 8 out of 9 have been returned to the community at about the age at which Dr Stein and Dr Susser would expect them to be capable of independence

It is interesting, too, to note that the authors, in estimating hostel needs, have made no provision for hostel accommodation for those who will in future be classified as severely subnormal —i e, those notified by education authorities to local health authorities Is it their view that severely subnormal persons are never suitable for hostel care, and that local health authorities have no duty to make provision for them in this way?

Brockhall
Langho, near Blackburn
D J ROSE

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THROMBOTEST

SIR,—Owren's thrombotest is rather expensive for utine use and an exact description for preparation of the agent has not yet been given With the help of the ncise indications in Owren's first publication [1] we were le to prepare a similar reagent using barium-sulphate-lsorbed ox-plasma, ox-brain thromboplastin, cephalin, d calcium-chloride solution

ethods

(1) *Adsorbed plasma* —Nine parts ox-blood were mixed with one rt 0 1 *M* potassium oxalate monohydrate, and centrifuged for 30 nutes at 2500 r p m The plasma was adsorbed with barium lphate 100 mg per ml for 5 minutes at 20°C and the barium lphate removed by centrifugation (30 minutes at 2500 r p m) he supernatant was neutralised with 0 5 *N* HCl to pH 7 35 ne-tenth volume of Owren's buffer (see 5 below) was added The lsorbed plasma was stored at 4°C overnight and centrifuged (30 nutes at 2500 r p m) The Quick-time of the adsorbed plasma was ore than 15 minutes

(2) *Ox-brain thromboplastin* —Approximately 300 g of ox-brain as washed free of blood and membranes with tap-water It was lended in a ' Mix-master ' for 2–4 minutes During this procedure 00 ml of saline 0 9% was added After one hour the mixture was entrifuged for 30 minutes at 2500 r p m and the supernatant eutralised to pH 7 35 with 0 5 *N* NaOH One-tenth volume of uffer was added and the reagent was diluted to the required strength ith buffer saline (one volume buffer to nine volumes of 0 9% NaCl) he strength was checked in a Quick system with normal plasma sing the ox-brain suspension as thromboplastin By means of a lution curve we determined at which dilution we obtained a Quick-me of 35–45 seconds

(3) *Cephalin* —A cephalin-suspension was prepared according to ilstone's technique as described by Hjort et al,[2] 100 g of human rain is washed free of blood and membranes and ground with 5 ml acetone After centrifuging the acetone was discarded and the esidue re-extracted with the same volume of acetone The procedure as repeated six times The residue was then extracted with 450 ml f ether overnight at room-temperature The ether was siphoned off nd evaporated to dryness by suction at 35°C The resulting residue as washed twice for 15 minutes with 225 ml of acetone and then edissolved in 50 ml of ether The ether was again evaporated to ryness and suction continued for 75 minutes The waxy brown esidue was suspended in 50 ml of Owren's buffer (see 5 below) This as centrifuged for 20 minutes at 1700 r p m and again for 10 inutes at 2500 r p m The supernatant milky white suspension was iluted with Owren's buffer We determined the dilution at which the Quick-time of normal plasma using cephalin as thromboplastin was 10–50 seconds

(4) *Calcium-chloride solution* —After systematic trials a 0 03 *M* olution of CaCl was selected

(5) *Owren's buffer* was prepared by mixing 11 75 g sodium diethyl-barbiturate, 14 67 g sodium chloride, and 430 ml 0 1 *N* HCl and ultimately adding distilled water to 2000 ml

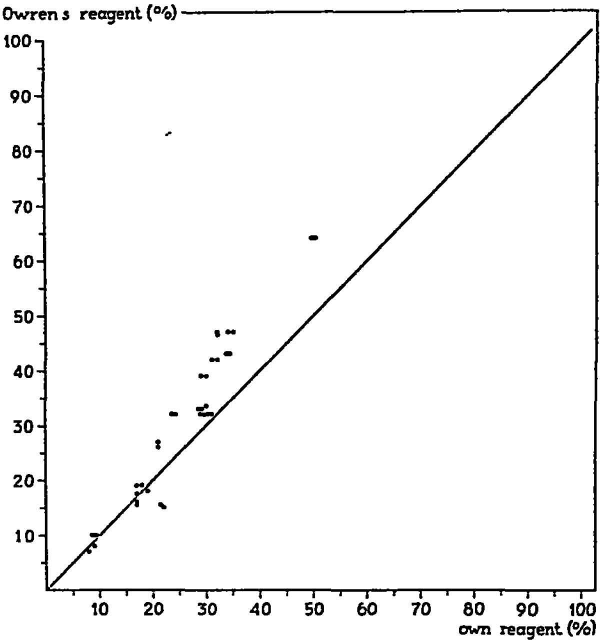

Fig 2—Comparison of reagents using blood of patients having anticoagulant therapy

Two parts of adsorbed ox-plasma and one part of 0 03 *M* CaCl$_2$ were mixed with one part cephalin and one part ox-brain thromboplastin After adding 0 1 ml citrated blood the volume of the mixture is 0 6 ml To obtain the same concentration of cephalin and ox-brain thromboplastin as determined sub 2 and 3, we had to take twice the concentration of these substances, the volume of the mixtures described sub 2 and 3 being 0 3 ml The mixture was lyophilised in portions of 0 5 ml wet volume and kept in vacuum-sealed ampoules Before use the reagent was dissolved in a 3 0 mM CaCl$_2$ solution to 0 5 ml The test was performed as indicated by Owren, adding 0 1 ml of citrated blood, kept in plastic tubes, to 0 5 ml of reagent.

Results

Thrombotest times were measured in serial dilutions of citrated normal blood. The blood was diluted with citrated saline (one part of citrate and nine parts of saline) The results obtained with the original thrombotest-preparation were compared with those obtained with the reagent prepared as described above (fig 1) In 70 samples of citrated blood of patients on long-term anticoagulant therapy we compared the thrombotest-method with the results obtained with our reagent (fig 2) As can be seen from the two figures there is a close and stable correlation between the two reagents compared

It can be said therefore, that a thrombotest-like preparation is not difficult to prepare It is scarcely more expensive than the reagents used in a one-stage Quick-test

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Holland.

H FROHN
C HAANEN
G MORSELT

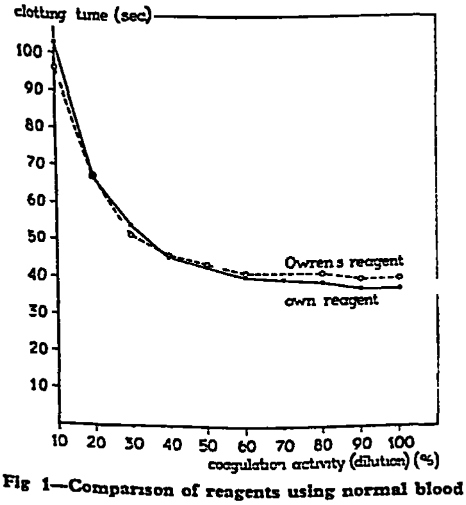

Fig 1—Comparison of reagents using normal blood

SIR,—A very interesting article [1] by Professor Owren describes a new method of controlling anticoagulant therapy I was greatly encouraged to see this article and to see the report [2] of the working party to the Medical Research Council on the same subject

I have been using long-term anticoagulant therapy for the past ten years and have used the Manchester method of controlling dicoumarol administration I learned this method from Dr Benjamin Manchester of the George Washington University School of Medicine in 1954 In

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[1] Owren, P A *Lancet*, 1959, ii, 754
[2] Hjort, P , Rapaport, S I., Owren, P A *J Lab clin. Med* , 1955, 46, 89

[1] Owren P A *Lancet*, 1959, ii, 754
[2] *Brit med J* 1959, i, 803

Farrar, V K Zworykin, and C Berkley derives its energy from radiofrequency signals beamed on to the pill from outside (A similar system is used, according to newspaper reports, for operating clandestine microphones in other people's embassies)

Transistors are now widely used in electrophysiological equipment, where their small size, tiny power consumption, and reliability are advantageous For a large saving in weight in electrocardiographs and electroencephalographs it is necessary to redesign the pen recorders or other display systems

Conventional methods for recording intracardiac pressures will be improved by pressure-sensitive probes (Telco) small enough (2 7 mm in diameter and 7 mm long) to be passed into the heart on the end of a catheter The probe has a good frequency response and can be used for phonocardiography

Transistor circuits and miniature components were two outstanding features of the conference A third was the resurgence of activity in ultrasonics as a diagnostic weapon Two groups showed scanning equipment using echo-sounding and television techniques to build up pictures of body sections Resolution and detail are poor by radiological standards, but the method may prove useful in obstetrics and gynæcology An ultrasonic rheograph, now available commercially in Japan, uses the Doppler effect to tackle the difficult problem of measuring flow-rate in an intact blood-vessel An ultrasonic signal, transmitted through the skin, is reflected by the moving blood with a small change in frequency from which the flow-rate may be determined (the same basic principle is used in the radar speed-meter now favoured by some police authorities)

Electronic devices have been used in clinical science for many years, and their uses will grow rapidly, but it would be wrong to expect too much from this field of research Enthusiasm for novel techniques of measurement can easily obscure important defects in the designer's knowledge or understanding of the processes under investigation Whether the right approach is obtained by encouraging people to specialise in two distinct subjects or by building teams capable of sharing freely ideas and experience is an open question Certainly the new electronic instruments will not achieve the fullest possible value unless their design proceeds alongside basic research on the relevant physiological mechanisms The human brain and nervous system are a network of transducers and amplifiers par excellence To improve them, or even to tamper with them in a meaningful way, is a formidable assignment. Pointing to an inconspicuous fellow-creature in the buffet, one member of the conference asked (with more wit than delicacy) "Where will you find so superb an example of automation, produced at little cost in large numbers by unskilled labour?"

University of Glasgow

The D P H has been awarded to the following

Agnes M Gordon, Irene R Jamieson, David Kennedy, Anne D Lindsay, Caecilia M Logan, Alexander Neilson Elizabeth M Park, Desmond J Reilly, Katherine S Scott, Norma E I Temple

Royal College of Surgeons of England

On Tuesday, Sept 6, at 5 P.M , at the college, Lincoln's Inn Fields, London, W C 2, Mr Harry Annamunthodo will give a Hunterian lecture He will speak on rectal lymphogranuloma venereum in Jamaica

King's College Hospital

On Friday, Oct 14, at 4 30 P M , at the medical school, Denmark Hill, London, S E 5, Sir James Paterson Ross will give the Thomas Percy Legg lecture He will speak on the principles of surgery

College of General Practitioners

Butterworth Gold Medal Essay Competition —The subject of this year's essay competition is Television and Health Entries should reach the chairman of the awards committee at the college, 41, Cadogan Gardens, London, S W.3 by Sept 17

New Ministry of Health Office in Liverpool

The Ministry have opened a regional office in Liverpool (Royal Liver Building, 4th floor, Liverpool, 3) Hitherto the work of the Manchester and Liverpool regions has been combined in a single office at Manchester Miss A E Earlam will continue as principal regional officer of the Manchester region, and Mr V F Jones has been appointed principal regional officer for Liverpool

Biochemical Society

The next meeting of this society, which is to be hel with the British Association for the Advancement of S at the Physiology Institute, Newport Road, Cardiff, on Se will take the form of a symposium on the organisa financing of research in biochemistry and allied scie Great Britain

London Hospital

On Monday, Sept 12, Prof Alrick B Hertzman, Louis University, Missouri, will give a lecture on respo the circulation to heat On Tuesday, Sept 13, Pro Herbert Hensel, University of Marburg, will give a lec specific and non-specific cutaneous receptors Both the l will be given at the medical college, Turner Street, E 5 15 P M , on the occasion of the second internation climatological congress

St Bartholomew's Hospital

Dr Alvin F Coburn, of New York, will give a lec Tuesday, Sept 27, at 5 30 P M , at the medical college, C house Square, London, E C 1 He will speak on a new in the *mechanism of rheumatic fever*

British Association of Physical Medicine

This association will hold its provincial autumn mee Saturday, Oct 8, at Brighton Further particulars may from the association, 47, Lincoln's Inn Fields, London,

Association of Industrial Medical Officers

The annual provincial meeting of this Association will at Southampton, from Sept 5 to 9 Applications for r tion should be sent to Dr R W R Beasley, Medical D ment, Southern Gas Board, 224, Winchester Road, Southa

International Congress on Mental Retardation

This congress will be held in Vienna from Aug 14 1961 Further particulars may be had from the congress Universitats-kinderklinik, Lazarettgasse 14, Vien Austria

Royal Free Hospital, London

On Wednesday, Sept. 7, Dr Donald W Seldin, of Texas, will speak on the syndrome of potassium defici man On Friday, Sept 9, Dr Frederic C Bartter, of Be will speak on aldosteronism Both lectures will be at 5 at the hospital, Gray's Inn Road, W C 1

Work Study

The Royal Institute of Public Administration is org a series of courses on this subject for officers in the service The first was held earlier this year under the di of Mr N B W Rose, formerly works study manager alkali division of Imperial Chemical Industries, Limite next two courses will be held from Oct 31 to Jan from Sept 4 to Nov 10, 1961 Candidates should be ated by their employing authorities and preference given to officers who will be employed full-time on wor duties Applications for the next course should be soon as possible to the director of the institute, Haldane 76a, New Cavendish Street, London, W 1

On Friday, Sept 30, at 3 P M at St George's Hospital School, Hyde Park Corner, London, S W 1, Field Marshal V Slim will give the annual inaugural address

On Monday, Oct 3, at 3 P M at Church House, Great Street, London, S W 1, the Very Rev E S Abbott, Dean o minster, will give the inaugural address to the Westminster School

On Thursday, Oct 13, at 3 P.M at the Beveridge Hall, House, London, W C 1, Lord Piercy will give the inaugural to the Charing Cross Hospital Medical School

The British Association of Pædiatric Surgeons will hold its meeting in 1961 in Stockholm from Sept 12 to 14

CORRIGENDUM *Fluoridation* —In our issue of Aug 20 (p 4 three concentrations given in the second paragraph under the Fluorine and Fluorides should have been 'parts per 1000 and so should the first item in the list on p 126

The Lancet · Saturday 10 September 1960

THE EVOLUTION OF MODERN OBSTETRICS *

SIR DUGALD BAIRD
M.D , B Sc , LL.D Glasg , F R C O G , D P H
EGIUS PROFESSOR OF MIDWIFERY AND GYNÆCOLOGY,
UNIVERSITY OF ABERDEEN

lasgow forty years ago, when I was a medical
t, childbirth was a dangerous and wasteful process
19,000 women admitted to the Glasgow Maternity
al between 1925 and 1929, 542 died Eclampsia
ed in 395 cases, with a maternal case-mortality of
There were 226 deliveries following craniotomy,
% of the mothers died Few medical students were
of all this death and destruction, since they were
n in the wards or labour rooms and never attended
ital clinics Clinical obstetrics consisted of (1)
in a large amphitheatre and watching our teachers
m cæsarean sections and various types of vaginal
ion, and (2) conducting domiciliary deliveries with
w student Since we were unsupervised and had
ed no practical instruction before setting out “ on
t ”, we were quite unable to render any effective
ent, nor were we allowed to give drugs to relieve
r check bleeding I can still recall vividly our feeling
dequacy, although fortunately the patients seemed
singly grateful for the little we did for them

t such experiences were not peculiar to Glasgow
wn by the following excerpt from a letter from Sir
y Holland

> he change since my student days is unbelievable! As I
> ayed on in the Anatomy and Physiology Departments
> my primary F.R C.S exam I arrived at the Hospital
> (or too early) to begin my surgical and medical dressing
> rking, so the Dean said ‘ Do your Midder and get it
> the way ’, which I did It was one month (with another
> t) on the Extern district There was no in-patient
> fery teaching, any obstetric emergencies were taken
> e Gyn ward.
>
> he Resident House Accoucheur showed me how to make
> and gave me a few tips, and, armed with these *plus*
> le red Herman ’ in my pocket, I went to live in a bedroom
> my fellow student) We had meals at the Hospital and
> loused ourselves, naked on a sheet, on the floor every
> The Hospital then was on one side of a big slum (now
> emolished)
>
> he first case I had was about midnight. The husband
> e to a room in a slum house where he and his family
> nd slept and he worked at boot-repairing I duly made
> when my finger was withdrawn it was covered with a
> horrid looking black stuff
>
> hinking something mysteriously dreadful must have
> ned in the poor woman’s inside, I hastened back to the
> ital to fetch the Resident Accoucheur I had gone only a
> e of hundred yards when I heard running feet behind me
> s the breathless husband who panted—‘ For Gawd’s
> Doc, come back, the baby’s bein’ born! ’ Back we tore
> found the body of the babe outside but the head still in
> must be what my ‘ little Red Herman ’ calls a breech
> ntation, said I I wrenched out the head as best I could,
> las, the babe was dead.
>
> That was the year 1901 A good bit of evolution since
> I guess! ”

the Glasgow Maternity Hospital, during the 1920s, we were dealing with a concentration of abnormal midwifery, the like of which has probably never been seen anywhere else in Britain, but the state of midwifery all over the country was bad, and national inquiries showed both in England and Wales and in Scotland that many deaths could have been avoided

In 1935, it became possible to take effective measures against sepsis, the greatest cause of maternal mortality at that time Other advances followed, and in many areas the maternal death-rate has now almost reached an irreducible minimum It might be thought that standards of obstetric care are now about optimal Yet the study of fœtal mortality indicates that we have no cause to be complacent, for example, in England and Wales, the stillbirth-rate is higher than in many other countries, and has been almost stationary for over a decade

Maternal Mortality

In the Glasgow Royal Maternity Hospital in the 1920s, there was an average of 2 maternal deaths every week, and we were so preoccupied with the problem of keeping the mother alive that the very high fœtal mortality was very seldom discussed

The City of Glasgow helped to pioneer the industrial expansion of the 19th century and became one of the places “where wealth accumulates and men decay” Many of its inhabitants lived in degradation, crowded together in tenement slums Few of the slum children, after weaning, ever drank milk except in the smallest quantities, and smoke from factories and domestic coal fires shut out the sun Rickets was so common that Glasgow surgeons became famous for their skill in performing osteotomy to straighten crooked legs, and obstetricians for their skill in the complicated vaginal operations made necessary by deformed pelvic bones To the extent that the long struggle against deficiency disease is virtually over, our population may now be considered well nourished, but minor degrees of malnutrition no doubt still exist and many of the mothers of today are stunted by the malnutrition they experienced as children during the 1930s

Rural areas escaped many of the ill effects of industrialisation, and country women were therefore taller, better developed physically, and generally healthier than those in the cities Despite this, examination of the maternal mortality statistics of thirty years ago shows that there was little difference in the overall rates of city and country districts In the rural areas the death-rate from puerperal sepsis was generally lower because the greater isolation of cases hindered the spread of the hæmolytic streptococcus Difficult labour due to disproportion was almost certainly less in rural areas But lack of specialist help, inadequate communications, and deficiencies in transport increased the mortality from such sudden and serious conditions as eclampsia and antepartum and postpartum hæmorrhage The advantages and disadvantages of rural life thus almost exactly cancelled each other out, giving an overall maternal mortality-rate not very different from that of the cities

The two main reasons for the excessive maternal mortality in the past were (1) ignorance of the causes of many of the serious complications of pregnancy and labour and the inadequacy of the methods of treatment

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e Ingleby lectures delivered in Birmingham on May 18, 1960 available, and (2) the lack of a well-organised maternity service staffed by well-trained doctors and midwives Until as recently as 1937, when the Maternity Services (Scotland) Act was passed, it was legal in Scotland for an untrained woman to attend a mother in labour for gain

Sepsis

By far the most important cause of maternal deaths, both in the cities and in country districts, was puerperal sepsis Even after a labour that had been entirely normal, a rigor on the second or third day, accompanied by a sudden rise of temperature and pulse, could mean death within a week from septicæmia or peritonitis The clinical features were well known to the women themselves and to the handywomen in attendance The profession was very reluctant to admit that the doctor or midwife was often the carrier of the streptococcus and indeed sometimes the primary source of the infection, yet in 1795, Alexander Gordon of Aberdeen, after a simple epidemiological investigation, had been able to say “ this disease seized such women only as were visited or delivered by a practitioner or taken care of by a nurse who had previously attended patients affected with the disease In short, I had evident proofs of its infectious nature ” (Quoted by Porter 1958)

Before 1935, research on methods of typing streptococci had made it possible to chart without doubt the source and mode of spread of the organism responsible for most cases of puerperal sepsis This led to the identification, control, and treatment of carriers among nurses, doctors, students, and others, the use of masks, and the immediate isolation of infected cases Although these measures led to some decrease in the incidence of streptococcal sepsis, it was difficult to get them carried out really effectively Fortunately the sulphonamides were introduced in Britain very soon afterwards

Penicillin, which is now used instead of the sulphonamides, is still remarkably effective against the streptococcus The rise in the incidence of drug-resistant organisms in most maternity hospitals in recent years has not, so far, increased the maternal death-rate from sepsis, but it has underlined the need to practise the principles of isolation and barrier nursing if maternity hospitals are to be kept safe for the mother and more especially the child In the overcrowded and understaffed hospitals of today we have come to rely too much on chemotherapy The need to design hospitals so that the risk of sepsis is reduced to a minimum is as important as ever it was It would be most unfortunate if outbreaks of sepsis should curb the work of our maternity hospitals at a time when they are capable of doing so much for the safety and comfort of the mother and baby

Hæmorrhage

The death-rate from hæmorrhage in Scotland did not begin to fall till after 1941, when blood-transfusion services based on blood-banks came into being, largely under the stimulus of war The rate of fall was most rapid after 1947, presumably because the ending of the war released for civilian duties large numbers of young doctors experienced in the treatment of acute hæmorrhage and shock

It is hard to realise how little blood was given twenty-five years ago, even in our large maternity hospitals Since blood-banks had not been invented, the only source of blood in emergency cases was relatives or friends of the patient—usually a very unsatisfactory and unreliable method of obtaining a supply In a series of 43 maternal deaths from postpartum hæmorrhage in Glasgow Maternity Hospital during the decade 1925- blood-transfusion was given only twice (Baird 1 Since 1948, regional blood-transfusion services have perfected Blood has become much more widely ava and standards of asepsis and of typing of blood have raised Despite these advances, antepartum and p partum hæmorrhage are still very much dreaded midwives and doctors, since even under the best c tions there are occasional fatalities

Toxæmia

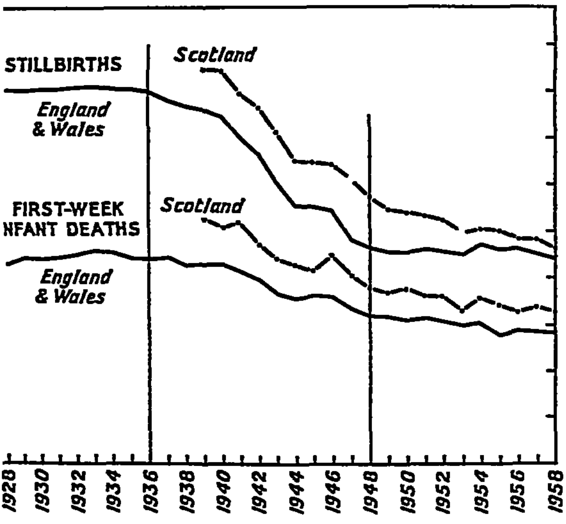
So little progress had been made in preventing d from eclamptic toxæmia before 1939 that many e tained serious doubts as to the value of antenatal ca the prevention of eclampsia It is worth remembe however, that in the Maternity Services (Scotland) of 1937, it was laid down, for the purpose of calcul the remuneration of the doctor, that three ante examinations should be carried out This was take some doctors as the optimum rather than the minim which makes it scarcely surprising that the ben derived from antenatal care conducted on these lines disappointing Bearing in mind that no specific cure pre-eclampsia has yet been discovered, the gradual steady fall in the death-rate since 1941 must be regar as satisfactory To minimise the damage done by disease we have to rely on a high and steadily impro standard of antenatal care This means very freq examinations and sometimes long-continued trea in hospital, all very costly in time and money Ne theless, these methods when applied conscientiously h almost abolished deaths from eclampsia and eclampsia and have greatly decreased the stillbirth in these conditions

Associated Conditions

Maternal deaths due to general medical or su conditions complicating pregnancy, especially he disease, used to be common, in addition, many de caused by such obstetrical abnormalities as tox prolonged labour, and hæmorrhage were predisposed by poor maternal health and physique

Another striking feature of those days was the la number of deaths associated with excessive childbear In the Glasgow Maternity Hospital in 1925–34 out 999 maternal deaths, 227 (27%) were in women who previously given birth to at least six children, and about 100 cases (about 10% of all deaths in the hospita the past obstetrical or medical history was so abnorm that further pregnancy should have been avoided at a costs (Baird 1936)

The report on a Confidential Enquiry on 1094 Matern Deaths occurring in England and Wales in 1925- (Wrigley 1957) showed that toxæmia had become t most important single cause of death The over maternal mortality had fallen to about one-sixth of th of 1932, nevertheless, a primary avoidable factor w present in not less than 43% of cases 10% of the wom who died of toxæmia had not made any arrangements f antenatal care or confinement Characteristically, th were elderly multiparæ, in whom the mortality from causes is well above average The most important si avoidable factor was the patient's failure to consu doctor Of the 1094 deaths, 153 (14%) followed abort and in 58 of these the abortion was known to have be procured by the mother herself The majority of abort were in married women whose circumstances w



1—Stillbirth and first-week infant death-rates England and 'ales 1928–58, Scotland 1935–58

cribed as poor Wrigley thought that these women ight have had a struggle to keep a home together l acted in the belief that they could not contemplate ther addition to the family "

For every death from procured abortion, large numbers other women go through a dangerous illness from ich they may never fully recover As Wrigley says, he problem is just as much a social problem as it is dical, but it is one which will have to be tackled oner or later all over the world "

Since Wrigley's report was published, maternal rtality has continued to fall and we are now able to y that, with a high standard of obstetric care and nscientious and cooperative patients, there should be w maternal deaths But it would be a mistake to conude that in the present state of knowledge they can be minated In Britain, at least, deaths still occur very casionally even under the best conditions, especially a result of eclampsia and hæmorrhage

Fœtal Mortality

Now that maternal mortality is so low, the death-rate mongst babies is regarded as a more satisfactory and ore sensitive index of the efficiency of maternity services he term perinatal mortality, defined as the number of illbirths and deaths in the first week after birth per 00 total births, is being used more and more in this nnection It is, of course, true that a few babies die om obstetrical causes after the end of the first week otably from malformations), and a few during the first eek from diseases acquired after birth (notably infecons) I shall use the stillbirth-rate in discussing certain pects of fœtal wastage But, on the whole, the perinatal ortality-rate gives a more convenient and comprehensive easure of the wastage of babies from causes associated ith childbearing The lack of improvement in our erinatal mortality rate since 1948 is particularly disppointing since it has coincided in time with the first ten ears of the National Health Service

Since 1935 in Scotland the rate of improvement in the illbirth and the first-week death-rate has been much ower than that for maternal mortality and the posteonatal mortality As already explained, the main causes f maternal mortality were amenable to direct treatment, nd advances in treatment such as the introduction of the antibiotics have achieved spectacular results By contrast, the unborn baby depends for its wellbeing mainly on the efficiency of the mother's reproductive system, although it fares remarkably well in times of privation, the obstetrician can at present do relatively little during the antenatal period to prevent such major causes of death as prematurity and what must, for want of a better term, be called " placental insufficiency "

Variations in the stillbirth-rate over the last thirty years will repay detailed study Fig 1 shows that in England and Wales between 1928 and 1933 it rose slightly, although during this period the maternity services were expanding The fact that unemployment was rising and reached its peak of 21 5% of the insured population in 1932 is probably significant After 1933 the stillbirth-rate began to fall, coinciding with a fall in unemployment. The rate of fall accelerated during the war years, when an enlightened food policy ensured adequate supplies of " protective " foods and vitamins for expectant and nursing mothers The fact that expectant mothers were treated as a priority group gave wide publicity not only to the importance of good nutrition during pregnancy but also to the need for good antenatal care The fall in the stillbirth-rate continued till 1948, with a temporary halt in 1945 and 1946 Since 1948 there has been practically no change

The variations in the first-week death-rate in England and Wales have resembled those of the stillbirth-rate but have been less in degree The patterns in Scotland have been similar except that the stillbirth-rate continued to fall slowly after 1948 and has now almost caught up with the English figure

Further evidence of the importance of the standard of living can be adduced by comparing trends in regions of England and Wales having different socioeconomic characteristics Fig 2 shows that the stillbirth-rate rose

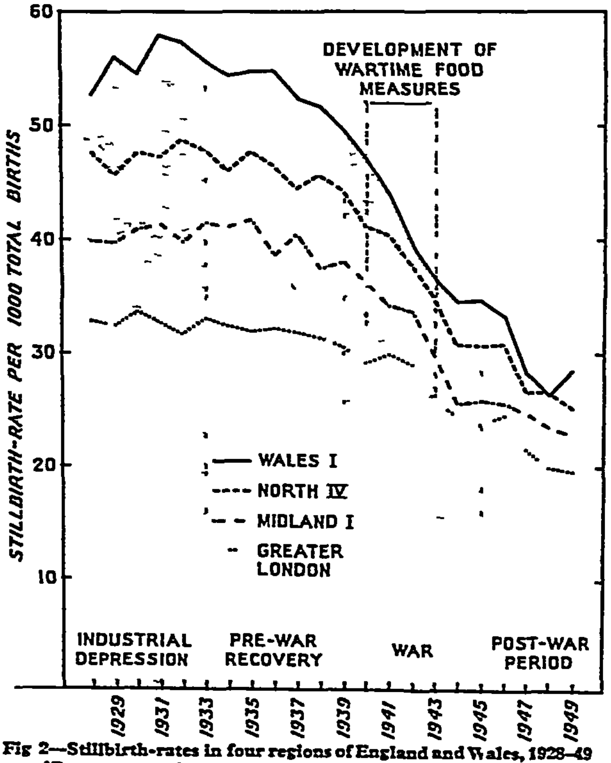


Fig 2—Stillbirth-rates in four regions of England and Wales, 1928–49
(*By courtesy of the* Journal of Obstetrics and Gynæcology)

appreciably in the two areas suffering most during the industrial depression of 1930–31—namely, Wales I and North IV—whereas there was only a small rise in London During the pre-war recovery period the greatest fall took place in Wales With the onset of war there was an immediate acceleration of the decline in the stillbirth-rate in Wales I and in North IV, while, by contrast, there was a slight increase in 1941 in London, followed by a lesser fall By the end of the war, the gap in the stillbirth-rates between the areas had greatly narrowed, which is what one would expect from the fact that war-time food policy raised the standards of diets most in the areas where it was worst before the war

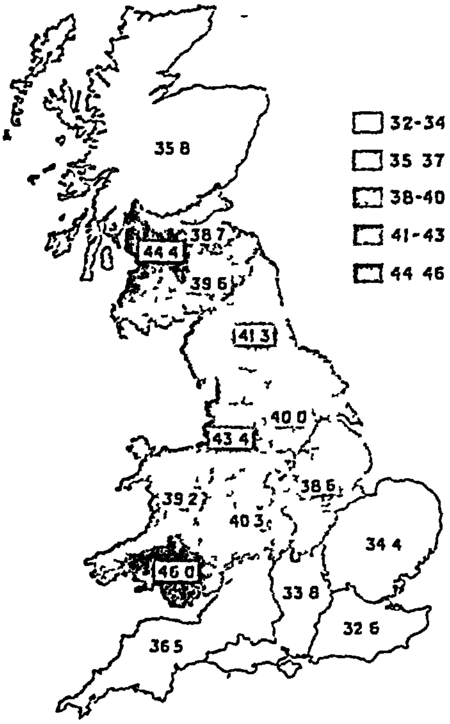


Fig 3—Perinatal-mortality rates Standard regions of England, Wales, and Scotland 1957

The war-time fall in the stillbirth-rate suggests strongly that the quality of the diet consumed during pregnancy has an important influence on the outcome of pregnancy (Duncan, Baird, and Thomson 1952) Some may feel that this conclusion should be tested directly by means of a controlled feeding experiment, but the difficulties of such a test make it impracticable If a change in mortality comparable to that achieved by the war-time food policy was to be expected, it would be necessary to use more than 5000 experimental subjects and a similar number of controls (Thomson 1959)

Fig 3 shows that in 1957 there were still considerable differences in perinatal mortality in different parts of Britain The regional differences are very similar to those for infant mortality, deaths from pulmonary tuberculosis, or deaths from any other disease associated with malnutrition and poor living conditions

Health and Physique

Why do these regional differences in perinatal mortality still persist? We have produced much evidence to show that perinatal mortality is greatly affected by the health and physique of the mother as well as by her diet during pregnancy in other words, the diet consumed from birth to maturity is at least as important as the diet taken during pregnancy (Thomson 1957)

The variations in health and nutrition which exist in Britain today are difficult to define and diagnose clinically, consequently we have used such indirect indices as social class and height It is known that the percentage of short women increases steadily with declining soc status, and in each social class tall women have lowe perinatal death-rates and prematurity-rates than shor women For example, in Aberdeen the percentage o primigravidæ who are 5 ft 4 in or more in height declin from 46 in social classes I and II to 21 in classes IV an V, and the percentages under 5 ft 1 in are 9 and 2 respectively

Fig 4 indicates the remarkable changes produced i prematurity- and perinatal-mortality rates by social cla and height The prematurity-rate varies from 3 8% i tall women in social classes I and II to 14 3% in sho women in classes IV and V The perinatal-mortality ra rises in exactly the same way, ranging from 14 5 per 100 in tall primigravidæ in the upper social classes to 55 p 1000 in short primigravidæ in the lowest social classes

These facts, backed by much more evidence which w have amassed, suggest that many women in Aberdee and probably in Britain as a whole, are short, not fo genetic reasons, but because they are physically stunte and physiologically inefficient Indeed, a simple guid to the general level of health of the women in a communit can be obtained by measuring heights and constructin a distribution curve from the data The variation i reproductive efficiency resulting from variations i maternal physique and health helps to explain some o the epidemiological facts For example, it explains wh in rural areas the perinatal mortality is often less than i the cities, despite much simpler maternity services

The effect of the interplay of these two fundamenta factors—namely, the health and physique of the patien and the standard of obstetric care—can be observed i many different situations For example, in 1956 when th stillbirth-rate in Denmark was 17, it was 15 in Copenhagen, 17 in the other towns, and 18 in the rural areas o Jutland Kaern (1958) has shown that in the rural areas although the prematurity-rate was low (5%) the stillbirth-rate was relatively high, because the scarcity o obstetricians and maternity hospitals in these area resulted in the death of babies from birth trauma an asphyxia which could have been avoided by a bette standard of care in labour In Copenhagen, on the othe hand, although the prematurity-rate was higher than i the rural areas (7%), birth trauma and asphyxia wer less frequent causes of death, because of a very hig

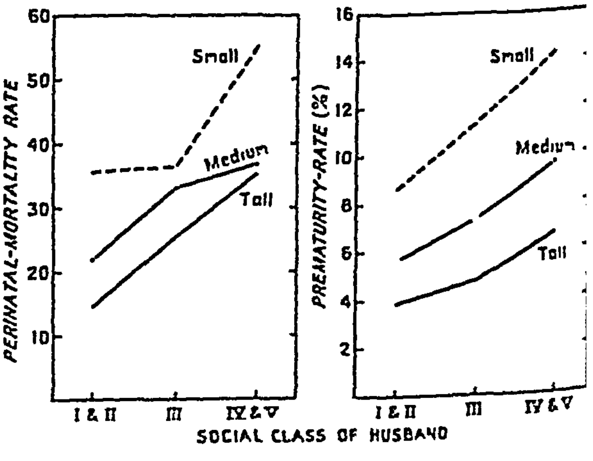


Fig 4—Perinatal-mortality and prematurity-rates by height and social class Aberdeen primigravidæ 1949–57 (Tall 5 ft 4 in. or more; small under 5 ft 1 in.)

standard of care in labour, and thus the very low stillbirth-rate of 15 was achieved

The stillbirth-rate in Denmark generally, and in Copenhagen in particular, is very low by British standards and could not be attained without a very high level of health of the whole population Some idea of this is obtained by the observation of Brandstrup (1958) that 67% of the women attending his obstetric clinic in Copenhagen measured 160 cm (5 ft. 4 in) or more in height, this is in striking contrast to the rate of 24% for Aberdeen primigravidæ.

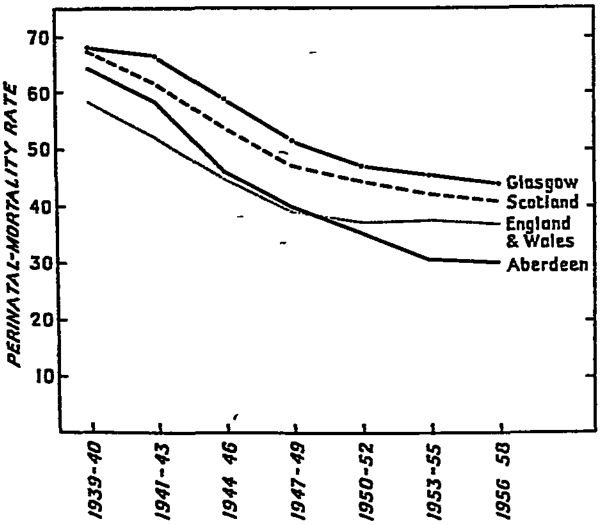


Fig 5—Perinatal-mortality rates England and Wales, Scotland, Glasgow and Aberdeen, 1939–58

Other evidence of the superior physique of the Danes is available Boyne and Leitch (1954) showed that the average height of young Servicemen in Denmark is now 174 4 cm (5 ft. $8^{1}/_{2}$ in) which is equivalent to that of young men in Britain coming from social classes I and II The average increase in height in Denmark between 1915 and 1956 was about $2^{1}/_{4}$ in. (5 4 cm)

There are no satisfactory observations of secular change in adult stature in Britain, but the increased rate of growth and in standard of health of schoolchildren, which is now occurring, should lead to an increase in the average stature of young adults When the present generation of children constitutes the majority of mothers, the perinatal mortality should decline

Standard of Care

We must, however, consider whether it is possible to lower perinatal mortality in the intervening years by improved standards of maternity care At first glance, the stationary perinatal-mortality rate in the past ten years suggests that little is possible It is highest in the heavily industrialised areas where the general level of health and physique is poor, which suggests that this factor imposes very definite limits to what can be done quickly But our experience in Aberdeen, where the overall standard of health, as judged by the average height of the women, is by no means high, suggests that many infant lives could be saved now by improved organisation of maternity services and a higher standard of care.

Fig 5 shows that the perinatal mortality in Aberdeen, which was appreciably higher than that for England and Wales before the war, has fallen considerably in the past ten years and is now about 20% less than that for England and Wales, 29% less than Scotland as a whole, and 37% less than Glasgow It seems reasonable to postulate that what has been done in one area and no doubt in several others could be done to a greater or lesser extent in the country as a whole To obtain further evidence on this point, the Aberdeen experience may be examined in more detail The perinatal mortality in Aberdeen fell from 45 in 1948 to 28 in 1958 In view of the small number of cases involved it is not possible to analyse the changes year by year, consequently two five-year periods, 1948–52 and 1953–57, have been used for further study of the decline over the ten-year period.

Fig 6 shows that the rate fell in first, second, and third pregnancies but not in fourth and subsequent pregnancies The improvement was greatest in primigravidæ, especially in those aged 30 or over, with the result that the well-known rise in perinatal mortality with age has now disappeared This reduction in mortality has, we believe, followed directly the application of the conclusions of our epidemiological and laboratory research into the causes of perinatal deaths For example, we found that the risks of death from birth trauma, asphyxia, and placental insufficiency, rise steadily with increasing age, particularly in primigravidæ This is especially true if the pregnancy lasts longer than 40 weeks Fortunately a high proportion of these " elderly " primigravidæ belong to the upper social classes and are tall and healthy, and consequently the risk of prematurity is small The main problem is to secure the safe delivery of the mature fœtus The fall in the perinatal mortality has been least in those under 25 years of age. Many women, especially in the youngest age-group, come from social classes IV and V, where prematurity and malformations, especially of the central nervous system, are common It must be noted, however, that in this age-group the full-time fœtus rarely dies from asphyxia, and the danger of prolonged pregnancy is slight, suggesting that some aspects of uteroplacental function are more dependent on the age of the patient than on her physique and general level of health Again, prolonged labour from uterine dysfunction is seldom seen in very young primigravidæ unless there is underlying disproportion, consequently birth trauma is not an

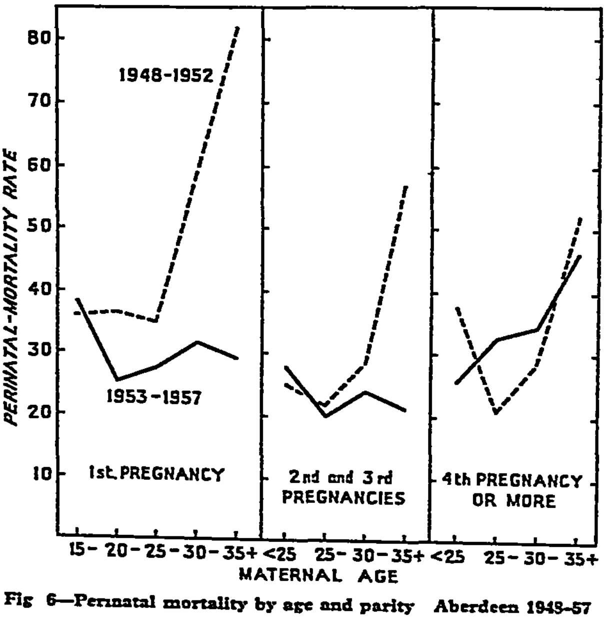


Fig 6—Perinatal mortality by age and parity Aberdeen 1948–57

important cause of perinatal mortality at this age The main problem in this group is clearly to improve the general health and physique

The women in the higher parity groups, amongst whom the perinatal mortality has not fallen, come largely from the lower social classes, and consequently prematurity is an important cause of death In addition, laxity of the abdominal wall predisposes to malposition and such conditions as prolapse of the cord Increasing age, malnutrition, and hypertension also predispose to intrauterine death Other factors to be taken into account in explaining our failure to reduce the perinatal mortality in this group are that the women often do not seek medical advice till the pregnancy is far advanced, and up to half of them choose home delivery They are therefore not directly under our care, whereas the vast majority of Aberdeen women having first, second, and third babies are confined in hospital

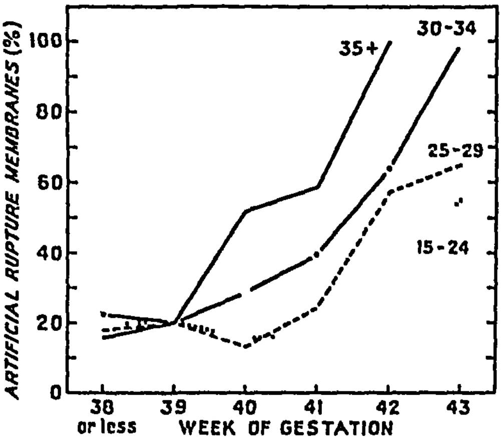


Fig 7—Incidence of artificial rupture of membranes by age and week of gestation Booked married Aberdeen primigravidæ 1953–57

Our investigations suggested that there is much to be said for induction of labour to avoid the risk of placental insufficiency, which increases with prolonged pregnancy, and for a more liberal use of cæsarean section to avoid undue stress to the baby in labour Fig 7 gives the incidence of surgical induction of labour in primigravidæ in 1953–57 It shows that in the age-group 35+ induction was performed in all those who had reached the 42nd week of pregnancy and in 55% of those reaching the 41st week, the younger the woman the lower the percentage having induction at each week of gestation The cæsarean-section rate in primigravidæ increased from 2 8% in 1948–52 to 4 6% in 1953–57

The table gives an analysis of cæsarean-section and perinatal-mortality rates in primigravidæ, by the age and height of the mother, in 1953–57. The cæsarean-section rate rises from 2 1% in tall women to 8 8% in short women, and from 2 2% in the age-group 15–19 to 32% in those aged 35 or more Tall women between the ages of 25–29 and 30–34 have the lowest perinatal mortality (about 10 per 1000), which is one-third of the average for all primigravidæ To secure these very low death-rates, however, cæsarean-section rates of 2 2 and 6 3% respectively in the two age-groups were considered necessary, most often because of prolonged labour due to uterine dysfunction or because of fœtal distress In the age-group 20–24, the perinatal mortality was higher (21 per 1000), but here the cæsarean-section rate was very low (0 5%), because in this group, as already stated, prolonged labour and placental insufficiency are uncommon, although the adverse social factors result in a higher perinatal mortality from prematurity, antepartum hæmorrhage, and malformation of the central nervous system—deaths which obviously cannot be prevented by increased use of cæsarean section In the age-group 15–19, where the perinatal mortality is 40 per 1000, the adverse social factors are even more important

EFFECT OF MATERNAL AGE AND HEIGHT ON CÆSAREAN SECTION AND PERINATAL-MORTALITY RATES

Booked Aberdeen primigravidæ, single births, 1953–57

Age	15–19	20–24	25–29	30–34	35+	All ages
Tall (5 ft 4 in and over)	0 8 *41*	0 5 *21*	2 2 *11*	6 3 *8*	17 1 *29*	2 1 *18*
Medium	0 7 *34*	2 0 *27*	5 1 *10*	14 0 *23*	31 9 *21*	4 0 *29*
Small (under 5 ft 1 in)	5 7 *52*	5 2 *27*	13 4 *45*	16 4 *18*	61 1 *0*	8 8 *31*
All heights	2 2 *41*	2 4 *25*	5 8 *25*	11 6 *20*	32 0 *27*	4 6 *27*

Perinatal mortality rates in italic figures

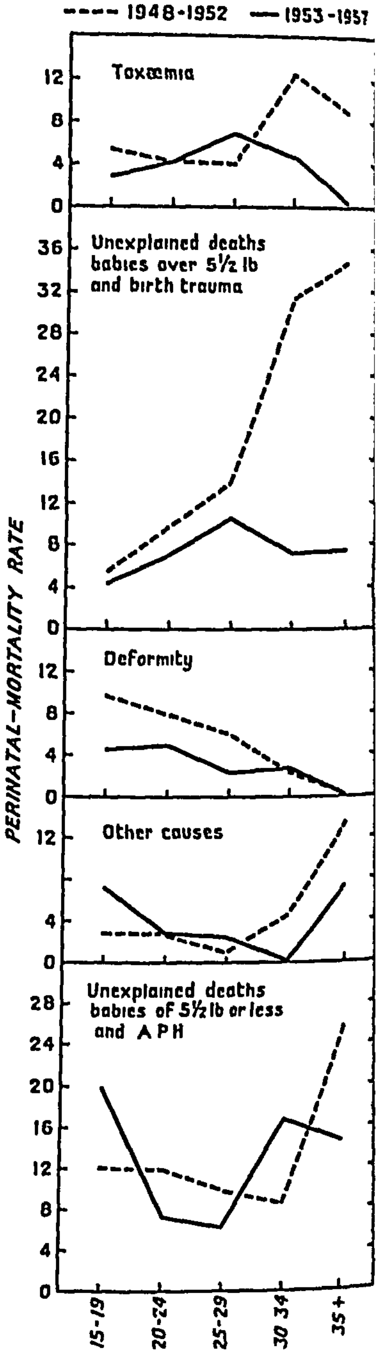


Fig 8—Perinatal-mortality rates by clinical cause and maternal age All Aberdeen primigravidæ 1948–52 and 1953 57

At all heights the cæsarean-section rate rises sharply in women of 35 years or more Even in tall women it rises from 6% in the age-group 30–34 to 17% in the 35+ age-group This is because, after the age of 35, deterioration of uterine and placental function, even in women of excellent health and physique, is so frequent, and the need to secure a live baby so great, that cæsarean section is performed if the baby is thought to be in any danger.

Fig. 8 shows that the most striking change between the first and the second five-year period is the reduction in unexplained and asphyxial deaths and those from birth trauma, especially in primigravidæ aged 30 or more. It is of some interest to note that the death-rate from these causes is now greatest in the age-group 25–29. This is explained by the fact that these women are sufficiently old for the increased risks of uterine and placental insufficiency to exist, but young enough to make one hesitate to employ induction and cæsarean section as freely as in the older women. There is also a substantial fall in the death-rate from toxæmia in the older women. The mortality associated with prematurity and ante-partum hæmorrhage has not fallen. We cannot take any credit for the fall in the incidence of deaths from malformations especially in younger primigravidæ, which was presumably due to chance.

The extent of the increased operative intervention which has been thought necessary to give these results is as follows. In primigravidæ aged 30 years or more the incidence of artificial rupture of the membranes increased from 13 to 35% and the cæsarean-section rate from 12 to 16%. This resulted in a reduction in the perinatal mortality from birth trauma, asphyxia and unexplained death of the full-time fœtus from approximately 27 to 10 per 1000. In the younger age-groups, the return in terms of a lowering of perinatal mortality was much less. Nevertheless, since a large proportion of primigravidæ are under the age of 25 (about 65%), the effect of a slight improvement in mortality in this age-group on the *overall perinatal-mortality rate* in primigravidæ is as great as a very much bigger reduction in mortality in the 10% of primigravidæ who are over 30.

Unfortunately surgical induction by rupture of the membranes increases the risk of infection, especially when labour does not follow the induction quickly, and occasionally a cæsarean section has to be done because labour fails to start despite every effort. There is no doubt also that, if the first child is delivered by cæsarean section, the second child is likely to be delivered by the same method. In addition, a cæsarean section performed in a first labour seems to act as a slight deterrent to future childbearing. Since the increased use of surgical induction and cæsarean section has undoubtedly saved infant lives, these drawbacks are not in themselves good reasons for discontinuing the method, unless it can be shown that the risk to the mother is thereby increased.

Between 1948 and 1957, 1665 cæsarean sections were performed in the Aberdeen Maternity Hospital with five maternal deaths. This rate, 0·3%, is of course much higher than the overall maternal mortality, but it must be remembered that the alternative to cæsarean section would often be a further prolongation of labour and a difficult forceps delivery. In fact, 3 of the 5 deaths occurred in cases where labour had lasted more than forty-eight hours and where the operation was performed because of maternal distress and not primarily to save the baby. Antibiotics and improved methods of treating shock and hæmorrhage would no doubt make vaginal delivery in such cases much safer than it was twenty years ago. A precise and up-to-date estimate of the risk cannot be given, since very few difficult vaginal deliveries after prolonged labour are now undertaken, but even if the maternal death-rate were low the incidence of morbidity would undoubtedly be high. The effect of avoiding damaging vaginal deliveries can be assessed from the fact that young women with extensive damage to the cervix, vagina, rectum, and bladder are seldom, if ever, seen nowadays in a gynæcological department.

Similarly, in considering the effect of difficult delivery on the baby, we have to assess, in addition to the immediate mortality, the risk of permanent damage in those who survive. Not surprisingly, the measures introduced in 1953–57, which have been so successful in preventing deaths from birth trauma and asphyxia, have also decreased the overall incidence and severity of asphyxia and have made resuscitation easier. It is important, however, to know whether the few born asphyxiated suffer any permanent damage as a result, since, if they do, still further efforts to avoid asphyxia at birth will be required. Recently Fraser and Wilks (1959) followed up, at the age of $7^{1}/_{2}$ years, a group of children who, born in 1948–50, had been severely asphyxiated at birth: these were carefully matched against a control group of babies born in excellent condition. Very little difference in the incidence of physical lesions or psychological disturbances in the two groups was found. These negative findings are most reassuring.

The *British Medical Journal* (1958), noting that there is at present no adequate method of assessing placental function, has said: "The obstetrician still has to rely on his clinical judgment in deciding afresh in each case whether induction of labour will be of benefit to the baby's health or not." In our experience, if the obstetrician relies entirely on his judgment of the individual case he will lose the occasional baby because "placental insufficiency" cannot be diagnosed reliably. The alternative is to perform numerous routine inductions of labour on the basis of epidemiological inference, and to use cæsarean section freely in the interests of the baby. On balance, we think that this policy has been justified in the absence of any more selective method of prevention. There is, of course, considerable difference of opinion in obstetrical circles about the dangers of prolonged pregnancy and the methods of avoiding them. It may be that the regime we have used is unnecessary and that just as good results can be obtained by a more conservative approach, but statistically sound evidence in support of conservatism has not so far been published in Britain. Figures for the City of Aberdeen have been given in some detail to illustrate the necessity for accurate statistical analyses of all the relevant facts if reliable conclusions are to be drawn about any method of treatment.

Conclusions on Perinatal Mortality

There is evidence that by improving the standard of the maternity services, the present perinatal-mortality rate of 36 in England and Wales and 39 in Scotland could be lowered to about 30 per 1000. In some areas, where the general level of health is good, it could be reduced below 30, but in the heavily industrialised areas this level might not be reached.

To reduce the national perinatal mortality much below 30 per 1000 would require a considerable improvement in the general level of health and physique. As schoolchildren have become taller and healthier in recent years, the outlook is hopeful. Earlier marriage, which is such a striking feature of post-war Britain, must make childbearing easier and safer, especially when accompanied by higher standards of health and physique. The tendency to avoid excessive childbearing, and especially if it is continued till after the age of 35, will also reduce the risks In time it should be possible to keep the national perinatal mortality to about 25 per 1000 with less difficulty than we experience in keeping the present rate at 36

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(To be concluded)

BACTERIOLOGICAL STUDIES ON A NEW PENICILLIN—BRL.1241

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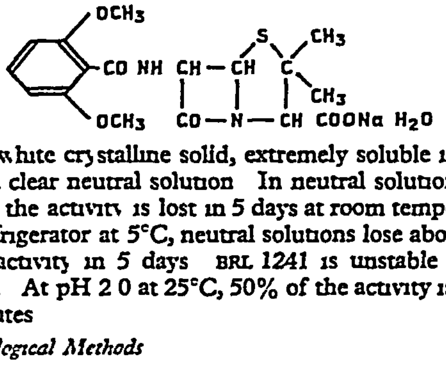
BRL 1241 is a new penicillin prepared from 6-aminopenicillanic acid* Unlike penicillin G and V, this penicillin is stable to staphylococcal penicillinase and is active against the penicillinase-producing penicillin-resistant staphylococci

Investigation

The compound is sodium 6-(2 6-dimethoxybenzamido) penicillanate monohydrate, with the structural formula



It is a white crystalline solid, extremely soluble in water giving a clear neutral solution In neutral solution about 50% of the activity is lost in 5 days at room temperature In a refrigerator at 5°C, neutral solutions lose about 20% of the activity in 5 days BRL 1241 is unstable in acid solution At pH 2 0 at 25°C, 50% of the activity is lost in 20 minutes

Bacteriological Methods

Minimum inhibitory concentrations required to prevent growth for 24 hours at 37°C were determined by serial dilution in nutrient broth ('Oxoid' no 2) and also in nutrient agar ('Oxoid' no 2) A concentration of 5% whole blood was incorporated in the media for the streptococci and pneumococci Serial dilution tests were normally inoculated with one drop of an overnight broth culture Serial dilutions in agar were poured into petri dishes and inoculated by streaking a loop from an overnight broth culture The effect of BRL.1241 on bacterial growth in broth was also measured by opacity readings in a 'Unicam' SP 600 Sensitivity of test organisms to antibiotics other than BRL 1241 and penicillin G was determined using 'Oxoid multodisks' Viable counts were made by preparing 10-fold dilutions in agar and colony counting In addition to viable counts, an assessment of bactericidal activity was also obtained by making a streak approximately 3 cm long on agar using a loop from each tube of a serial dilution in broth Where the resulting growth of such streaks consisted of relatively few isolated colonies the number of colonies was recorded

Tolerance to BRL 1241, and the rate at which tolerance developed on exposure to BRL.1241, was determined by daily transfer from serial dilutions in broth using as inoculum for the next series the tube with the highest concentration of BRL 1241 permitting growth

Penicillinase

Studies were made using penicillinase produced by *Bacillus cereus* 569/H (N C T C 9945) and also the penicillinase produced by a culture of *Staphylococcus pyogenes* BRL 1083 *B cereus* was grown overnight in shaken flasks at 37°C and the cell-free culture fluid used as enzyme A suitable dilution of this enzyme was made as required *Staph pyogenes* BRL.1083 was grown in nutrient broth in shaken flasks at 37°C for 6 hours and BRL 1241 (0 5 μg per ml) was added as an inducer of penicillinase formation Incubation was then continued overnight, and the whole culture, including the cells, was used as enzyme BRL 1241 was used as an inducer because it is stable to penicillinase and is more effective than penicillin G or V

Results

Minimum Inhibitory Concentrations

The minimum concentrations required to inhibit growth of bacteria (M I C) for 24 hours at 37°C are shown in table I The penicillin-resistant staphylococci in this table were both resistant to penicillin G, 125 μg per ml, in this type of test Like penicillin G and V, BRL 1241 is active chiefly against the gram-positive bacteria and such gram-negative bacteria as *Neisseria catarrhalis* The compound shows very little activity against the gram-negative bacilli Activity against the staphylococci is independent of resistance to penicillin G, the highly resistant strains showing the same order of sensitivity to BRL 1241 as the penicillin-sensitive strains

Activity of BRL 1241 against a wider range of penicillin resistant staphylococci is shown in table II All the cultures were coagulase-positive cultures of *Staph. pyogenes* recently isolated in hospitals Most of them

TABLE I—MINIMUM INHIBITORY CONCENTRATIONS OF BRL.1241 FOR GROWTH OF BACTERIA
Cultures incubated for 24 hours

Species	Strain	M.I C. (μg per ml.)	
		Serial dilution in agar	Serial dilution in broth
Escherichia coli	BRL.1008	>250	
Proteus vulgaris	NCTC 401	>250	
Salmonella typhi	NCTC 8393	>250	>250
S typhimurium	BRL.1076	125	
Shigella shigae	NCTC 4837	250	
Aerobacter aerogenes	NCTC 418	>250	
Pseudomonas pyocyanea	BRL.1058	>250	
Neisseria catarrhalis	NCTC 3622	0·25	
Sarcina lutea	NCTC 8553	0·025	
Diplococcus pneumoniae	BRL.1221	0·05	0·06
" "	BRL.1223	0·05	
" "	BRL.1224	0·5	
" "	NCTC 7465	0·25	
Streptococcus pyogenes β type	BRL.1230	0·5	0·5
" " " "	BRL.1231	0·05	
" " " "	BRL.1275	0·05	
" " " "	BRL.1320	0·25	
" " " "	BRL.1321	0·06	
Strep viridans	BRL.1246	0·12	0·25
" "	NCTC 779	0·12	
" "	BRL.1323	0·12	
" "	BRL.1326	0·6	
" "	NCTC 3165	0·25	
Strep faecalis	BRL.1207	50·0	
Corynebacterium hofmanni	CTC 8338	0·6	0·12
Staphylococci, penicillin-sensitive			
Oxford staphylococcus	BRL.1227	1·25	1·25
Staph pyogenes	NCIB 6558	1·25	
" "	BRL.1270	2·5	
" "	BRL.1402	1·25	
" "	BRL.1409	1·25	
Staphylococci, penicillin-resistant			
Staph pyogenes	BRL.1063	2·5	2·5
" "	BRL.1059	2·5	2·5

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* Beecham Research Laboratories trade name for BRL.1241 is 'Celbenin'

TABLE II—MINIMUM INHIBITORY CONCENTRATIONS OF BRL.1241 FOR GROWTH OF PENICILLIN-RESISTANT STAPHYLOCOCCI
(Serial dilutions in agar)

Culture	Phage-type	Resistance pattern *						M.I.C. (µg per ml)	
		C	E	N	O	S	T	Penicillin G	BRL.1241
Staph aureus (Oxford)		—	—	—	—	—	—	0·02	1·25
Staph pyogenes BRL.1083	No known type	—	—	—	—	——	+—	125·0	2·5
" " BRL.1089	80	—	—		—	——	+—	125·0	2·5
" " BRL.1112		+	—	—	—	——	——	125·0	1·25
" " BRL.1113		—	—	—	—	——	—+	125·0	1·25
" " BRL.1105		—	—	—	—	——	+—	125·0	2·5
" " BRL.1091	80	—	—		—	——	——	62·5	2·5
" " BRL.1111	80	—	—	—	—	——	—	50·0	2·5
" " BRL.1093	54—	—	—		—	——	—+	50·0	2·5
" " BRL.1094	54+	—	+		—	——	—+	50·0	2·5
" " BRL.1095	80	—	—		—	——	—	25·0	2·5
" " BRL.1099	80	—	—	—	—	——	——	12·5	2·5
" " BRL.1104		—+	++	+—	——	——	—+	12·5	2·5
" " BRL.1090	79/53/54/77	—	—	—	—	—	—	10·0	2·5
" " BRL.1098	80	—	—	—	—	++	—+	5·0	2·5
" " BRL.1096	80	—	—	—	+	+—	+—	5·0	1·25
" " BRL.1097	80	+	—	—	—	—+	——	5·0	2·5
" " BRL.1100	80	—	—	—	—	—+	+—	5·0	2·5
" " BRL.1101	80	—	—	—	—	—	—+	5·0	2·5
" " BRL.1102	80	+	—	—	+	++	—	5·0	2·5
" " BRL.1085	58/80	—	—	—	—	—	—	2·5	1·25
" " BRL.1108		—	—	—	—	—	—	2·5	1·25
" " BRL.1084	42E	—	—	+	—	—	—	1·25	1·25

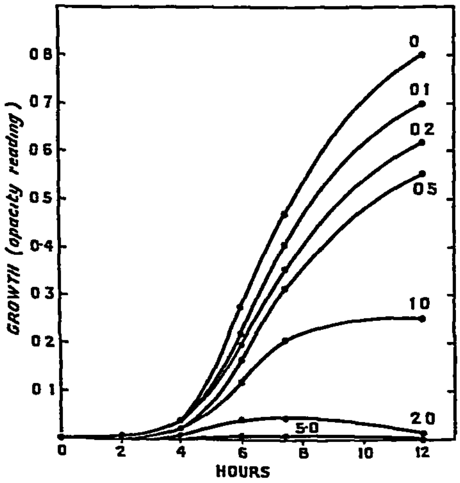
* C = chloramphenicol 10 µg
N = novobiocin 5 µg
S = streptomycin 10 µg

E = erythromycin 10 µg
O = oleandomycin 5 µg
T = tetracycline 10 µg.

— denotes sensitive
+ denotes partially resistant
—— denotes highly resistant

were phage-type 80 and resistant to one or more antibiotics as well as to penicillin. The results in table II show that activity of BRL 1241 is independent of resistance to other antibiotics as well as penicillin. All the strains were sensitive to BRL 1241 in concentrations of 1·25 to 2·5 µg per ml. Resistance of these cultures to penicillin G ranged from 1·25 to 125 µg per ml.

Growth curves for a penicillin-resistant culture of *Staph pyogenes* BRL 1083, in broth culture with different concentrations of BRL 1241 are shown in the figure. BRL 1241 was added at time 0 and 0·1 ml. of an overnight broth culture was used to inoculate 100 ml. of nutrient broth in 250 ml. shaken flasks which were incubated at 37°C. Growth was measured by opacity in the Unicam at 450 mµ. A concentration of 2·0 µg per ml. almost completely prevented growth and a concentration of 1·0 µg per ml. reduced growth to about 30% of the control.



Effect of BRL.1241 on growth of *Staph pyogenes* BRL.1083 (penicillin-resistant) in nutrient broth at 37°C. The figures on each curve indicate the concentration of BRL.1241 in µg per ml.

Effect of Inoculum Size

With cultures of penicillin-resistant staphylococci, the M.I.C. with penicillin G is greatly affected by the size of the inoculum. The results in table III show that inoculum size has very little effect on the activity of BRL 1241. This would be expected, since BRL 1241 is not destroyed by staphylococcal penicillinase.

Bactericidal Activity

The bactericidal activity of BRL 1241 is shown in table IV.

Broth cultures of *Staph pyogenes* BRL 1083 (penicillin-resistant) were incubated at 37°C for 3 hours, by which time a light growth was clearly visible. Compound BRL 1241 was then added in different concentrations and incubation continued. Viable counts were made at the time of addition of BRL 1241 and at intervals thereafter. A concentration of 2·5 µg BRL 1241 per ml. reduced the viable count from 44 million cells per ml. to 123 cells in 30 hours and a concentration of 5·0 µg per ml. reduced the viable count from 44 million cells per ml. to 90 cells in 5 hours.

Bactericidal activity was also assessed by streaking out on agar a loop from serial dilution cultures in broth. The broth cultures were carried out using plain nutrient broth and also broth containing 40% human serum. BRL 1241 was added to give serial dilutions and the broths inoculated with one drop of a 1/10 dilution of an overnight culture of the Oxford staphylococcus and also *Staph pyogenes* cultures BRL.1083 and BRL 1093. Viable streaks of the broths made immediately after inoculation resulted in heavy confluent growth in the streaks. After incubation at 37°C overnight, the streaks were again

TABLE III—EFFECT OF INOCULUM SIZE ON THE ACTIVITY OF BRL 1241 IN SERIAL DILUTION IN BROTH

Inoculum	M.I.C. (µg per ml.)	
	Oxford staph.	*Staph. pyogenes* BRL.1083 *
Overnight broth culture		
1 drop	1·25	2·5
1 drop of dilution 1 in 100	0·6	2·5
1 drop of dilution 1 in 1000	0·6	1·25
1 drop of dilution 1 in 1,000,000	0·5	1·25

* Penicillin-resistant.

TABLE IV—BACTERICIDAL ACTIVITY OF BRL 1241 AGAINST *Staph pyogenes* BRL 1083 (PENICILLIN-RESISTANT)

BRL.1241 (µg per ml.)	Viable counts (organisms per ml.)			
	0 hour	3 hours	5 hours	30 hours
0	44×10^6	148×10^6	$>100\times10^{11}$	$>100\times10^{11}$
2·5		100×10^4	189×10^3	123
5·0		60×10^3	90	4
10·0		76×10^2	58	0

TABLE V—BACTERICIDAL ACTIVITY OF BRL 1241 IN BROTH WITH AND WITHOUT THE PRESENCE OF HUMAN SERUM

Serial dilution broth cultures were inoculated with 1 drop of a 1-in-10 dilution of an overnight culture and incubated for 24 hours at 37°C. Viable streaks were then made on agar and the subsequent growth recorded.

Staph. pyogenes BRL 1083 and BRL 1093 were both highly resistant to penicillin.

BRL 1241 (µg. per ml.)	Oxford staph.		*Staph. pyogenes* BRL 1083		*Staph. pyogenes* BRL 1093	
		+40% serum		+40% serum		+40% serum
0·1	+++	+++	+++	+++	+++	+++
0·25	+++	+++	+++	+++	+++	+++
0·5	++	++	+++	+++	+++	+++
1·0	8	24	+++	+	+++	++
2·5	0	3	0	0	26	17
5·0	0	0	0	0	0	0
10·0	0	0	0	0	0	0

+++ = heavy confluent growth
++ = light confluent growth
+ = semi-confluent growth
numbers = actual numbers of colonies in the streak

made from each tube and the resulting growth recorded after incubation overnight. The results are shown in table V. With the Oxford staphylococcus a concentration of 1·0 µg. per ml. resulted in viable streaks showing only a very few colonies and the presence of 40% human serum did not significantly diminish this effect. With the cultures of penicillin-resistant *Staph. pyogenes* a concentration of 2·5 µg. per ml. resulted in none, or very few, colonies in the viable streaks, and again serum had no effect.

Thus, the compound appeared to be bactericidal at concentrations only very slightly higher than the minimum inhibitory concentrations.

Effect of Serum

Human serum does not diminish the activity of BRL 1241 either in liquid or in solid culture. The minimum inhibitory concentration of the compound in the presence of 40% human serum is the same as that in the absence of serum. Similarly, the bactericidal activity of BRL 1241 is not diminished by the presence of serum. The results shown in table V, which illustrate the bactericidal activity of BRL 1241, show that in the presence of 40% human serum the bactericidal activity is certainly not significantly less than it is in the absence of serum, and in certain of the experiments with the penicillin-resistant staphylococci it appeared to be even slightly greater.

BRL 1241 in Combination with Penicillin G

Experiments were carried out on the activity of mixtures of penicillin G and BRL 1241 in different proportions. The results showed no evidence of synergism, or antagonism, between the two antibiotics either against the Oxford staphylococcus or against cultures of penicillin-resistant staphylococci.

TABLE VI—DEVELOPMENT OF TOLERANCE TO BRL 1241

Cultures were transferred daily from serial dilutions in broth, the last tube showing growth being used as inoculum for the next transfer.

No. of transfers	M.I.C. (µg. per ml.)				
	Penicillin G	BRL 1241			
	Oxford staph.	Oxford staph.	BRL 1083*	BRL 1093*	BRL 1089*
0	0·01	2·5	2·5	2·5	2·5
1	0·05	2·5	5·0	2·5	5·0
2	0·06	5·0	5·0	5·0	5·0
3	0·12	6·2	5·0	6·2	6·2
4	0·25	6·2	6·2	6·2	6·2
5	0·25	12·5	6·2	6·2	6·2
6	0·25	25·0	6·2	6·2	6·2
7	0·6	25·0	6·2	12·5	6·2
8	1·2	25·0	6·2	12·5	12·5
9	2·5	25·0	5·0	6·2	6·2
10	2·5	25·0	12·5	12·5	12·5
11	2·5	25·0	12·5	25·0	25·0
12	1·2	12·5	12·5	25·0	25·0
13	2·5	25·0	12·5	25·0	25·0
14	5·0	25·0	12·5	25·0	25·0
15	5·0	25·0	12·5	25·0	25·0

* Penicillin-resistant cultures of *Staph. pyogenes*.

Resistance to BRL 1241

Prolonged incubation of serial dilution tests, both in broth and in agar, did not materially alter the M.I.C. of BRL 1241 against cultures of penicillin-resistant staphylococci. There was no evidence, therefore, that such cultures include resistant members of the population which are able to grow up after long periods. Experiments were also carried out with the surviving colonies which grew in viable streaks from broth cultures which had been incubated with concentrations of BRL 1241 which killed over 99·9% of the original populations. When tested against BRL 1241, these cultures showed the same sensitivity as did the original cultures and did not represent resistant strains. Among all the cultures of penicillin-resistant staphylococci tested, naturally occurring strains resistant to BRL 1241 were not encountered.

Tolerance to BRL 1241 does develop very slowly in vitro when cultures are repeatedly transferred in broth containing BRL 1241.

In the results shown in table VI, three strains of penicillin-resistant staphylococci were transferred daily in broth cultures containing BRL 1241 as described under the heading of Investigation. In addition, the Oxford staphylococcus was also transferred in the same way in broth containing BRL 1241 and also in broth containing penicillin G. The M.I.C. for each of fifteen transfers was recorded. Tolerance to BRL 1241 developed only very slowly and not to a very great extent. Tolerance by the Oxford staphylococcus to penicillin G developed considerably quicker. After fifteen transfers the penicillin-resistant staphylococci showed a 5–10-fold increase in tolerance to BRL 1241, whereas after the same number of transfers the Oxford staphylococcus showed a 500-fold increase in tolerance to penicillin G. Those cultures which gained in tolerance to *BRL 1241 as a result of repeated transfer* in broth containing this compound did not lose any tolerance when subsequently taken through six transfers in plain broth. The same cultures also retained their coagulase-positive character and showed the same degree of resistance to penicillin G as did the original cultures. Estimation of penicillinase production showed no significant difference between cultures which had developed some tolerance to BRL 1241 and the original cultures. Growth of the BRL 1241-tolerant cultures however, was *significantly slower than the normal cultures*.

TABLE VII—STABILITY OF BRL 1241 TOWARDS STAPHYLOCOCCAL PENICILLINASE

Staph. pyogenes BRL 1083 was grown in nutrient broth in the presence of 0·5 µg. BRL 1241 per ml. 5 ml. of the overnight culture was added to 5 ml. of phosphate buffer pH 6·0 containing penicillin G or BRL 1241 to give a final concentration of 1 mg. per ml. Enzyme reaction allowed to proceed at 37°C.

Time (minutes)	Penicillin G (µg. per ml.)	BRL 1241 (µg. per ml.)
0	1000	1000
5	330	1000
10	0	1000
20	0	1000
40	0	1000
60	0	1000

Cross-resistance

Cross-resistance typically occurs between antibiotics having similar chemical structure. Since BRL 1241 is a penicillin, cross-resistance would not be expected with other antibiotics in common use, and the results in table II show that there is certainly no cross-resistance between BRL 1241 and chloramphenicol, erythromycin, novobiocin, oleandomycin, streptomycin, and tetracycline

TABLE VIII—STABILITY OF BRL 1241 TOWARDS *B cereus* PENICILLINASE

Overnight broth filtrate of *B cereus* 569/H was used as enzyme. 2·0 ml was added to 8 0 ml of phosphate buffer pH 6 4 containing penicillin G or BRL 1241 to give a final concentration of 2 mg per ml Incubated at 37 C

Time (minutes)	Penicillin G (µg per ml.)	BRL 1241 (µg per ml)
0	2000	2000
1	0	1740
2	0	1610
3	0	1500
4	0	1400
5	0	1330

Stability to Penicillinase

Using staphylococcal penicillinase prepared as described under Investigation, no inactivation of BRL 1241 could be demonstrated after 60 minutes' incubation The same enzyme, under the same conditions, completely inactivated a solution containing 1 mg penicillin G per ml. in 10 minutes Stability of BRL 1241 to staphylococcal penicillinase was unaffected by pH Results with staphylococcal penicillinase are shown in table VII

Using *B cereus* penicillinase, some inactivation of BRL 1241 took place but at a very much slower rate than with penicillin G The pH optimum for *B cereus* penicillinase and BRL 1241 is sharper and lower (6 2–6 4) than for penicillin G (6 5–7 0) Results for inactivation of BRL 1241 with *B cereus* penicillinase are shown in table VIII With *B cereus* penicillinase there is an initial rate of inactivation which is faster than the subsequent rate This may be due to a low rate of breakdown of enzyme-substrate complex. Preliminary studies on the kinetics of inactivation with *B cereus* penicillinase indicate a K_m of approximately 0 5 mg per ml.

BRL 1241 induces formation of penicillinase Using a penicillinase-producing culture of *Staph pyogenes* BRL 1083, the maximum induction occurred with a concentration causing significant inhibition of growth When the inducer was added as described under Investigation, the optimum concentration was 0 5 µg per ml

Inactivation of penicillin G by staphylococcal penicillinase was found to be unaffected by the presence of BRL 1241 There was no evidence of competitive inhibition by BRL 1241 with staphylococcal penicillinase With *B cereus* penicillinase, on the other hand, BRL 1241 does competitively inhibit the inactivation of penicillin G Equimolar concentrations of BRL 1241 and penicillin G show a rate of penicillin-G inactivation only 10% of that in the absence of BRL 1241

Discussion

The outstanding property of this penicillin BRL 1241 is the stability to staphylococcal penicillinase and the resulting activity against the penicillin-resistant staphylococci Cultures of staphylococci resistant to concentrations of penicillin G as high as 125 µg per ml are almost as sensitive to BRL 1241 as is the Oxford staphylococcus Many of the penicillin-resistant staphylococci tested were phage-type 80, and all were sensitive to BRL 1241 at a concentration of 1 25–2 5 µg per ml These results have been confirmed by Elek and Fleming (1960), Knox (1960), Stewart et al (1960) and Thompson et al (1960) Penicillin BRL 1241 also shows the desirable properties of being bactericidal at concentrations only slightly higher than the minimum inhibitory concentrations and also of being unaffected by the presence of serum

Although primarily of value because of its activity against penicillin-resistant staphylococci, BRL 1241 also shows relatively high activity against many other pyogenic gram-positive cocci The cultures of β-hæmolytic streptococci tested showed a sensitivity of 0 05–0 25 µg per ml. and the cultures of *Streptococcus viridans* of 0 12–0 6 µg per ml With cultures of *Diplococcus pneumoniæ* the M.I.C was 0 05–0 5 µg per ml These results have been confirmed by Knox (1960) and Stewart et al (1960) Against the gram-negative bacilli, BRL 1241 shows even less activity than penicillin G

Naturally occurring strains of *Staph pyogenes* resistant to BRL 1241 have not been encountered, and this has also been the finding of the other workers cited above Development of tolerance in vitro, which does occur slowly, is of doubtful importance clinically, since this type of resistance to penicillin does not occur in vivo Although tolerance to penicillin G can develop in vitro, the only penicillin-resistant staphylococci isolated clinically are those strains which are resistant because they produce penicillinase This is not a character acquired as a result of exposure to penicillin the penicillinase-producing strains are merely selected out by the presence of penicillin. Resistance to BRL 1241 comparable to that which exists to penicillin G would require the ability to inactivate BRL 1241 by a new penicillinase Since cultures have not been encountered showing this property, it seems unlikely that the selection and proliferation of resistant strains will take place rapidly, if at all. In support of this it has been reported that resistant cultures have not been isolated after the clinical use of BRL 1241 (Elek and Fleming 1960, Stewart 1960)

Excluding the penicillin-resistant strains, BRL 1241 is not as active against *Staph pyogenes* as is penicillin G or V Activity is, however, of a similar order to that of many of the other antibiotics in current use, and adequate blood-levels are readily achieved (Knudsen and Rolinson 1960)

Summary

BRL 1241 is a new synthetic penicillin which is stable to staphylococcal penicillinase and active against penicillin-resistant staphylococci

All the cultures of *Staphylococcus pyogenes* tested were sensitive to BRL 1241 in concentrations of 1 25–2 5 µg per ml, regardless of their resistance to penicillin G and other antibiotics

BRL 1241 is also active against other pyogenic gram-positive cocci including β-hæmolytic streptococci, *Streptococcus viridans*, and *Diplococcus pneumoniæ*

BRL 1241 is bactericidal at concentrations only slightly higher than the minimum inhibitory concentrations, and activity is not diminished in the presence of serum

Cultures of *Staph pyogenes* became tolerant to BRL 1241 very slowly in vitro when subcultured in broth containing this antibiotic, but this does not seem to happen in vivo, and naturally occurring resistant strains have not been encountered

Although stable to staphylococcal penicillinase, BRL 1241 is inactivated by *Bacillus cereus* penicillinase, but at a very much slower rate than penicillin G BRL 1241 induces formation of penicillinase With *B cereus* penicillinase, BRL 1241 competitively inhibits inactivation of penicillin G, but this does not occur with staphylococcal penicillinase.

We are indebted to Dr J Farquharson, director of research, for his interest in the work, to Miss J Guy and Miss E Widden for technical assistance, and to the directors of Beecham Research Laboratories Limited for permission to publish

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TABLE V—BACTERICIDAL ACTIVITY OF BRL 1241 IN BROTH WITH AND WITHOUT THE PRESENCE OF HUMAN SERUM

Serial dilution broth cultures were inoculated with 1 drop of a 1-in-10 dilution of an overnight culture and incubated for 24 hours at 37°C. Viable streaks were then made on agar and the subsequent growth recorded.

Staph pyogenes BRL 1083 and BRL 1093 were both highly resistant to penicillin.

BRL.1241 (µg per ml)	Oxford staph		*Staph pyogenes* BRL.1083		*Staph pyogenes* BRL.1093	
		+40% serum		+40% serum		+40% serum
0·1	+++	+++	+++	+++	+++	+++
0·25	+++	+++	+++	+++	+++	+++
0·5	++	++	+++	+++	+++	+++
1·0	8	24	+++	+	+++	++
2·5	0	3	0	0	26	17
5·0	0	0	0	0	0	0
10·0	0	0	0	0	0	0

+++ = heavy confluent growth
++ = light confluent growth
+ = semi confluent growth
numbers = actual numbers of colonies in the streak

made from each tube and the resulting growth recorded after incubation overnight. The results are shown in table V. With the Oxford staphylococcus a concentration of 1·0 µg per ml resulted in viable streaks showing only a very few colonies and the presence of 40% human serum did not significantly diminish this effect. With the cultures of penicillin-resistant *Staph pyogenes* a concentration of 2·5 µg per ml resulted in none, or very few, colonies in the viable streaks, and again serum had no effect.

Thus, the compound appeared to be bactericidal at concentrations only very slightly higher than the minimum inhibitory concentrations.

Effect of Serum

Human serum does not diminish the activity of BRL 1241 either in liquid or in solid culture. The minimum inhibitory concentration of the compound in the presence of 40% human serum is the same as that in the absence of serum. Similarly, the bactericidal activity of BRL 1241 is not diminished by the presence of serum. The results shown in table V, which illustrate the bactericidal activity of BRL 1241, show that in the presence of 40% human serum the bactericidal activity is certainly not significantly less than it is in the absence of serum, and in certain of the experiments with the penicillin-resistant staphylococci it appeared to be even slightly greater.

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Experiments were carried out on the activity of mixtures of penicillin G and BRL 1241 in different proportions. The results showed no evidence of synergism, or antagonism, between the two antibiotics either against the Oxford staphylococcus or against cultures of penicillin-resistant staphylococci.

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No of transfers	M.I.C. (µg per ml)				
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4	0·25	6·2	6·2	6·2	6·2
5	0·25	12·5	6·2	6·2	6·2
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7	0·6	25·0	6·2	12·5	6·2
8	1·2	25·0	6·2	12·5	12·5
9	2·5	25·0	5·0	6·2	6·2
10	2·5	25·0	12·5	12·5	12·5
11	2·5	25·0	12·5	25·0	25·0
12	1·2	12·5	12·5	25·0	25·0
13	2·5	25·0	12·5	25·0	25·0
14	5·0	25·0	12·5	25·0	25·0
15	5·0	25·0	12·5	25·0	25·0

* Penicillin-resistant cultures of *Staph pyogenes*

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Prolonged incubation of serial dilution tests, both in broth and in agar, did not materially alter the M.I.C. of BRL 1241 against cultures of penicillin-resistant staphylococci. There was no evidence, therefore, that such cultures include resistant members of the population which are able to grow up after long periods. Experiments were also carried out with the surviving colonies which grew in viable streaks from broth cultures which had been incubated with concentrations of BRL 1241 which killed over 99·9% of the original populations. When tested against BRL 1241, these cultures showed the same sensitivity as did the original cultures and did not represent resistant strains. Among all the cultures of penicillin-resistant staphylococci tested, naturally occurring strains resistant to BRL 1241 were not encountered.

Tolerance to BRL 1241 does develop very slowly in vitro when cultures are repeatedly transferred in broth containing BRL 1241.

In the results shown in table VI, three strains of penicillin-resistant staphylococci were transferred daily in broth cultures containing BRL 1241 as described under the heading of Investigation. In addition, the Oxford staphylococcus was also transferred in the same way in broth containing BRL.1241 and also in broth containing penicillin G. The M.I.C. for each of fifteen transfers was recorded. Tolerance to BRL 1241 developed only very slowly and not to a very great extent. Tolerance by the Oxford staphylococcus to penicillin G developed considerably quicker. After fifteen transfers the penicillin-resistant staphylococci showed a 5–10-fold increase in tolerance to BRL 1241, whereas after the same number of transfers the Oxford staphylococcus showed a *500-fold* increase in tolerance to penicillin G. Those cultures which gained in tolerance to BRL 1241 as a result of repeated transfer in broth containing this compound did not lose any tolerance when subsequently taken through six transfers in plain broth. The same cultures also retained their coagulase-positive character and showed the same degree of resistance to penicillin G as did the original cultures. Estimation of penicillinase production showed no significant difference between cultures which had developed some tolerance to BRL 1241 and the original cultures. Growth of the BRL 1241-tolerant cultures, however, was significantly slower than the normal cultures.

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Staph pyogenes BRL 1083 was grown in nutrient broth in the presence of 0·5 µg BRL 1241 per ml. 5 ml of the overnight culture was added to 5 ml of phosphate buffer pH 6·0 containing penicillin G or BRL 1241 to give a final concentration of 1 mg per ml. Enzyme reaction allowed to proceed at 37°C

Time (minutes)	Penicillin G (µg per ml)	BRL.1241 (µg per ml)
0	1000	1000
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20	0	1000
40	0	1000
60	0	1000

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Cross-resistance typically occurs between antibiotics having similar chemical structure. Since BRL 1241 is a penicillin, cross-resistance would not be expected with other antibiotics in common use, and the results in table II show that there is certainly no cross-resistance between BRL 1241 and chloramphenicol, erythromycin, novobiocin, oleandomycin, streptomycin, and tetracycline

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Overnight broth filtrate of *B cereus* 569/H was used as enzyme 2 0 ml was added to 8 0 ml of phosphate buffer pH 6 4 containing penicillin G or BRL 1241 to give a final concentration of 2 mg per ml Incubated at 37°C

Time (minutes)	Penicillin G (µg per ml)	BRL 1241 (µg per ml)
0	2000	2000
1	0	1740
2	0	1610
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Summary

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BRL 1241 is also active against other pyogenic gram-positive cocci including β-hæmolytic streptococci, *Streptococcus viridans*, and *Diplococcus pneumoniæ*

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Cultures of *Staph pyogenes* became tolerant to BRL 1241 very slowly in vitro when subcultured in broth containing this antibiotic, but this does not seem to happen in vivo, and naturally occurring resistant strains have not been encountered

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CHEMOTHERAPEUTIC STUDIES ON A NEW ANTIBIOTIC—BRL.1241

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The discovery and isolation of 6-aminopenicillanic acid (Batchelor et al. 1959) has made it possible to synthesise a wide range of penicillins with modified properties. One of these, BRL. 1241,* has proved highly effective against penicillin-resistant staphylococci.

Methods and Results

In the following experiments BRL. 1241 and penicillin G were administered as their sodium salts.

General Pharmacology

In mice and cats no toxic symptoms were observed with single doses of 2·5 g. per kg. intravenously, and in mice and rats with doses of 4 g. per kg. subcutaneously. When BRL. 1241 was administered daily to rats for twelve weeks at doses of 100 and 500 mg. per kg. subcutaneously, and to dogs for four weeks at 250 mg. per kg. twice daily subcutaneously, no biochemical, hæmatological, or histological abnormalities were noted. Apart from the discomfort of the injection, the compound was well tolerated. 1% and 10% solutions were injected intramuscularly and intradermally into rats, guineapigs, and rabbits without any local irritation. Similarly, a 1% solution applied daily to the eyes of rabbits was without effect. Administration to anæsthetised cats at a dose of 500 mg. per kg. had no effect on blood-pressure and respiration.

Blood-levels in rabbits and dogs after intramuscular injection resembled those following injection of penicillin G. The mechanism of excretion in chicks was also similar to that of penicillin G. Like penicillin G, BRL. 1241 penetrates the blood-brain barrier only with difficulty. It is protein-bound to a lesser degree than penicillin G.

Protection Tests

The protective effect of BRL. 1241 was determined in mice infected with *Klebsiella pneumoniæ*, *Salmonella typhimurium*, *Diplococcus pneumoniæ*, *Staphylococcus pyogenes* Smith and *Staph. pyogenes* 52-75, the last organism being highly resistant to penicillin G (minimal inhibitory concentration 125 µg. per ml.).

Of the first four organisms, serial dilutions of 18-24-hour cultures were prepared in 5% hog gastric mucin to enhance the virulence, and 0·5 ml. volumes were injected intraperitoneally. Deaths were recorded over four days and the number of organisms killing 50% of the mice was estimated (L.D.$_{50}$). The mice under test were injected with a hundred times this number of organisms.

Penicillin G and BRL. 1241 were administered subcutaneously to groups of 10 mice in graded doses to the log base 4, in 0·2 ml. saline immediately following the infection. The mice were observed for four days and the deaths were recorded daily. The percentage deaths were plotted against log dose, and the dose of compound (mg. per kg.) giving protection to 50% of the mice (C.D.$_{50}$) was read off from the graph. The estimate of the C.D.$_{50}$ against *Staph. pyogenes* 52–75 was carried out in exactly the same way, except that 0·5 ml. of a 1/2 dilution in 5% hog gastric mucin of an overnight culture was used to infect the animals.

The results obtained are given in the table.

A further estimate of the in-vivo effect against penicillin-resistant organisms was carried out using the meth described by Selbie and O'Grady (1954). Groups of 1 mice (18–22 g.) were infected by injecting into the mus sheath of the thigh 0·2 ml. of a 1/2 dilution of an overnight growth of *Staph. pyogenes* Russell (type 80). BRL. 1241 i doses of 50, 100, and 200 mg. per kg. and penicillin G 200 mg. per kg. were administered subcutaneously daily for three days, the first injection being given immediately following the infection. An infected control group received no treatment. The maximum thigh diameter of each mouse was measured with callipers on the first, third, and eighth day after the infection. The results (fig. 1) clearly demonstrate a graded response to dose. The activity against other resistant staphylococci has been confirmed.

C.D.$_{50}$ VALUES FOR BRL.1241 AND PENICILLIN G DETERMINED IN MICE
(10 PER DOSE LEVEL)

Organism	C.D.$_{50}$ (mg. per kg.)	
	BRL. 1241	Penicillin G
Klebsiella pneumoniæ	Inactive	Inactive
Salmonella typhimurium	Inactive	Inactive
Diplococcus pneumoniæ	10·0	1·0
Staphylococcus pyogenes Smith	1·3	0·2
Staph. pyogenes 52–75 (penicillin-resistant)	100·0	Inactive

The activity of BRL. 1241 was further confirmed by a subsequent series of experiments, using the technique of Selbie and O'Grady (1954), in which groups of 10 mice were infected with two strains of staphylococci. *Staph. pyogenes* Russell (resistant to penicillin G) was injected into the muscle sheath of the right hind leg, and *Staph. pyogenes* 2187 (sensitive to penicillin G) was injected into the left hind leg. Because untreated mice usually died from this double infection, two control groups were used, one receiving the sensitive strain in the left leg, and the other receiving the resistant strain in the right leg. Th

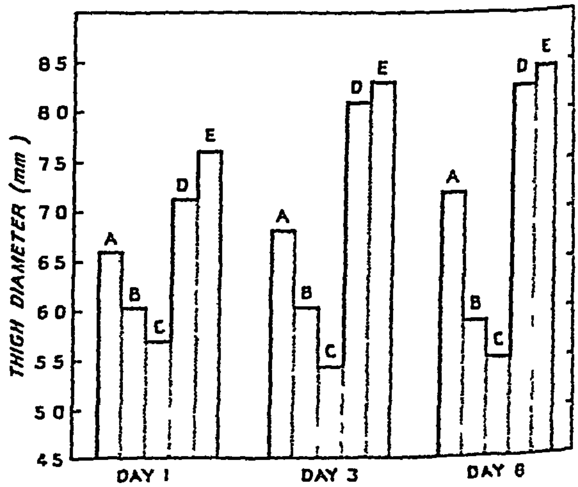

Fig. 1—Mean thigh diameters of mice (10 per group) infected intramuscularly with *Staph. pyogenes* Russell (penicillin-resistant). The following doses were administered subcutaneously daily for three days.

Group A —BRL.1241 50 mg. per kg.
" B — " 100 " " "
" C — " 200 " " "
" D —Penicillin G 200 " " "
" E —Untreated infected control

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* Celbenin is the registered trade name of Beecham Research Laboratories Ltd. for BRL. 1241.

thigh diameters were measured as described above Penicillin G and BRL 1241 were administered subcutaneously at a dose of 100 mg per kg daily for three days The results (fig 2) show the effectiveness of BRL 1241 in mice infected simultaneously with both resistant and sensitive staphylococci Penicillin G is completely inactive against the resistant strain, but more effective than BRL 1241 against the sensitive strain

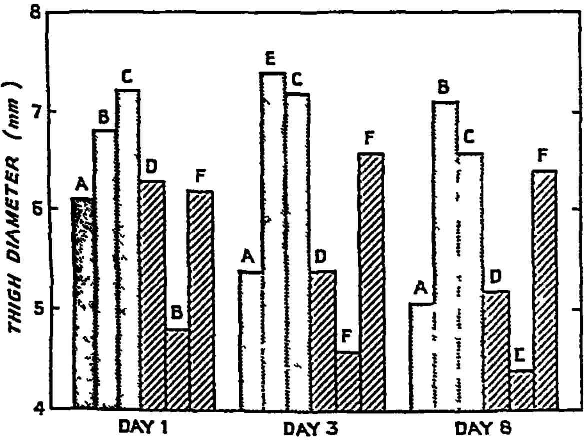

Fig 2—Mean thigh diameters of mice (10 per group) infected intramuscularly with *Staph pyogenes* Russell (penicillin-resistant) in the right hind limb and *Staph pyogenes* 2187 (penicillin-sensitive) in the left hind limb

BRL.1241 and penicillin G, 100 mg per kg, were administered subcutaneously daily for three days

Blocks A, B, and C are the mean thigh diameters of the limb infected with the resistant staphylococcus, and D, E, and F are the mean diameters of the limb infected with the sensitive staphylococcus Group 1 (A and D) received BRL.1241, group 2 (B and E) received penicillin G, and group 3 (C and F) was the untreated infected control

Conclusion

BRL 1241 is remarkably free from toxic actions It can be given in high doses intramuscularly or intravenously The blood-levels obtained after an intramuscular injection in rabbits and dogs follow a pattern very similar to that obtained after penicillin G Like penicillin G, it requires large doses before it will penetrate into the cerebrospinal fluid.

BRL 1241 does not combine with serum protein to the same degree as penicillin G This, however, does not seem to have influenced the cross-allergenic response in patients already sensitive to penicillin (Stewart et al 1960)

It is highly effective against staphylococci resistant to penicillin G, and the results obtained clearly demonstrate the activity in vivo Though BRL 1241 is not as effective as penicillin G against sensitive strains of staphylococci, its activity is still considerable In mice infected with both penicillin-sensitive and penicillin-resistant strains of staphylococci, it was equally active against the two organisms, whereas penicillin G was active only against the sensitive strain This is in agreement with the in-vitro findings of Knox (1960), Rolinson et al (1960), Stewart et al (1960) and Thompson et al (1960)

We wish to thank Prof C A Keele for his general interest and helpful discussions, Dr A A G Lewis, physician to the Connaught Hospital, Walthamstow, under whose skilled guidance the dog studies were conducted, and Mr F P Doyle and his colleagues for the preparation of the compound In addition, we wish to acknowledge the excellent technical assistance of Mr D Wright and Mr M J Wilson

References at foot of next column

A NEW TECHNIQUE FOR THE CONTROL OF HOSPITAL CROSS-INFECTION

EXPERIENCE WITH BRL.1241 IN A MATERNITY UNIT

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THE problem of cross-infection with staphylococci in hospitals is still largely unsolved While the treatment of cases is an important aspect, the fundamental requirement is to interfere effectively with the epidemiological cycle Rigorous aseptic surgical technique can keep wound infection to a low level but does not eradicate it Moreover it cannot be applied to the prevention of such forms of cross-infection as staphylococcal bronchopneumonia in elderly and debilitated patients Other things being equal, the greater the pollution of the environment by staphylococci, the more readily will wounds and weakened epithelial surfaces become infected High nasal-carriage rates in normal people, combined with the confined conditions in a hospital, lead to a build-up of staphylococci in the surroundings the noses of fresh individuals then become colonised in their turn and void more staphylococci into the air and dust This is the fundamental cycle, the patient being but an accident within it, but once sepsis has become established it also contributes staphylococci to the pool The introduction of antibiotics has not abolished this cycle, but has tended to eliminate drug-sensitive organisms Thus the environmental pool of infection has come to consist increasingly of staphylococci resistant to various antibiotics

It is our belief that the crux of the problem lies in nasal carriage An observation made by Gould in 1958 suggested that the atmosphere of hospitals contains appreciable amounts of penicillin demonstrable by air sampling, and he concluded that this accounted for the exclusion of penicillin-sensitive staphylococci from the noses of hospital personnel Since the nose appears to be the main site of multiplication, we decided to make use of this observation in our attempt to break the epidemic cycle Whereas penicillin excludes only staphylococci which are sensitive to it, leaving others free to multiply, the deliberate introduction into the atmosphere of an antibiotic active against *all* strains of pyogenic staphylococci should completely abolish the nasal carriage of this organism The spraying of a concentrated solution of such a drug should produce droplet nuclei of the antibiotic, which would follow essentially the same pathways as the staphylococci in the environment If an adequate concentration could be achieved on the nasal mucosa, the main source of staphylococci would be cut off, and the concentration of staphylococci in the surroundings would gradually diminish This in turn should lead to a reduction in cross-infection

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The drug of choice for this purpose should be highly active against *all* pyogenic staphylococci Its continued use should not lead to the emergence of resistant strains It must not be irritating or cause hypersensitivity phenomena

BRL 1241* is a synthetic derivative of 6-aminopenicillanic acid which retains the biological activity of penicillin but is invulnerable to staphylococcal penicillinase (Rolinson et al 1960) Its properties were studied by us to assess its suitability for the kind of use envisaged To test our general hypothesis we selected a maternity unit for aerial spraying, since infants are born bacteriologically sterile and regularly acquire *Staphylococcus pyogenes* in the nose by inhalation

Experiments

PROPERTIES OF BRL 1241

Bacteriostatic effect —We have confirmed the statement of Rolinson et al (1960) that strains of *Staph pyogenes* are sensitive to concentrations of 1 5 to 3 μg per ml 400 strains from routine isolations were tested, and without exception they were all sensitive to this dose The material consisted largely of strains resistant to various other antibiotics, as shown in fig 1 It is noteworthy, however, that a number of coagulase-negative micrococci were encountered which were resistant to this concentration

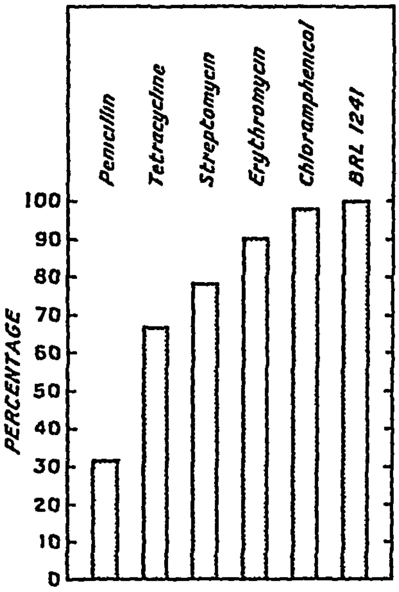

Fig 1—Sensitivities of 400 strains of staphylococci isolated from inpatients and outpatients

Bactericidal effect —The antibiotic is, moreover, highly bactericidal at a concentration of 6 μg per ml (fig 2) A 99 9% reduction of the viable count of a large inoculum (10^8) was achieved within ten hours Lysis of the organisms occurred in the presence of 5 μg per ml in broth cultures, as indicated by optical density measurements

Emergence of resistant strains —As naturally occurring resistant strains were not found, attempts were made to encourage the emergence of resistant mutants 12 strains of various phage groups showing multiple resistance to other antibiotics were subjected to 20 serial passages on gradient plates (Szybalski and Bryson 1952) containing BRL 1241 This method is known to reveal resistant mutants readily, but no mutants resistant to BRL 1241 were found All 12 strains showed approximately the same sensitivity in broth cultures after the 20 passages as they had shown before In some instances there were colonies on areas of gradient plates containing an apparently high concentration of the drug, but when these were subcultured on nutrient agar and tested they showed their original sensitivity

Other properties —The drug is a white crystalline odourless powder, readily soluble in water A solution containing 1000 μg per ml lost all activity in two days at 37°C in five days at 22°C, and in eight days at 10°C Solutions kept frozen were stable for several weeks The dry powder is stable at ordinary room temperature For our purposes it was more convenient to keep solutions frozen than to dispense the powder each time

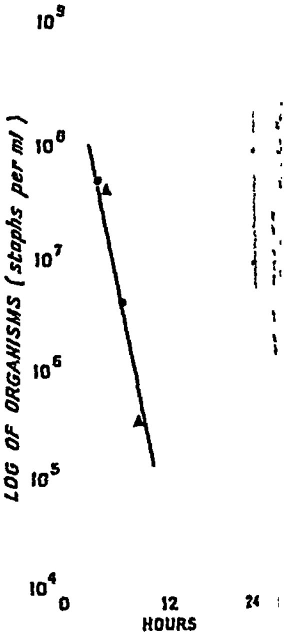

Fig 2—Effect of BRL.1241 on the viable count of two strains of *Staph pyogenes* (6 microgrammes per ml)

EFFECT ON STAPHYLOCOCCAL CARRIAGE

Nasal Carriage in Unit Before Treatment

The maternity unit contained two practically identical sections, ward A and ward B Each consisted of a ward and nursery and they were separate physically, but shared their nursing staff Normally the babies were nursed with their mothers Ward A together with its nursery occupied approximately 15,000 c ft

As a preliminary investigation, nasal swabs were taken daily from 29 babies born consecutively in ward A until *Staph pyogenes* was isolated It was assumed that they remained carriers for the rest of their stay in hospital (fig 3A) To test this point, 29 consecutive infants were similarly swabbed every day for 10 days in ward B The results in fig 3B show that the assumption is broadly correct It can be seen that the staphylococcal nasal carriage of the infants in both wards was over 50 of all the swabs taken This is in agreement with the findings of others (Cunliffe 1949) All but 1 of the strains of staphylococci isolated from these babies were resistant to penicillin, and about half were also resistant to other antibiotics

EFFECTS OF SPRAYING

Effect on nasal carriage —The first experiment consisted of spraying in ward A 1 0 gramme of the drug dissolved in 20 ml of distilled water from a universal container fitted with a 'Spraydex' plastic window-cleaning spray unit The fluid was sprayed as evenly as possible over all parts of the ward and nursery (fig 4) This took about two minutes Spraying was done once a day and nasal swabs were taken daily as before The results are shown in fig 3C There was a reduction in the number of positive isolations from 50 to 24% There was also a very marked reduction in the number of colonies grown from positive swabs

Spraying 1 0 g four times a day was next tried, after a short break, on another series of 29 babies The results are shown in fig 3D Though there was a further reduction in the isolations of *Staph pyogenes* to 12 4% of all swabs, it was noticed that all the isolations occurred during the first six weeks of this experiment, suggesting a cumulative effect Hence the experiment was continued for a further 29 babies without a break The results (fig 3E) revealed only 6 positive isolations out of 290 nasal swabs, and some of these were only single colonies The noses of most of the babies had become colonised, however, by coagulase-negative micrococci Many of these were resistant to BRL.1241 Some colonisation by gram-negative flora was also observed

Effect on umbilical and rectal carriage —This was no studied

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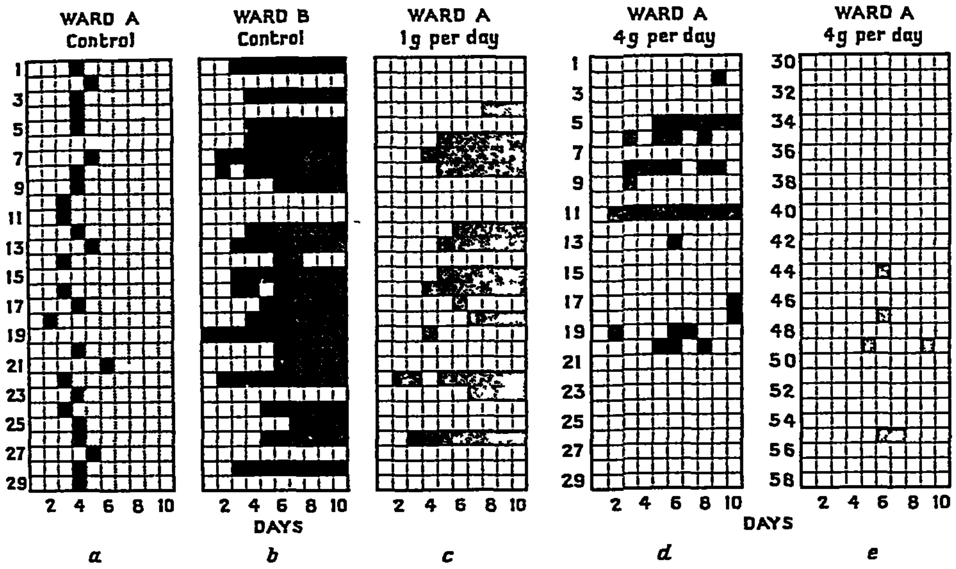
* This drug is marketed by Beecham Research Laboratories Ltd under the registered trade name Celbenin It was previously referred to by us as AB 1241 (Lick and Fleming 1960)



ig 3—Nasal carriage of *Staph pyogenes* by newborn infants showing the effect of spraying BRL.1241

Each figure represents the results of daily swabbing of a series of 29 babies.

Each horizontal column represents one baby and each square represents one day.

The days on which staphylococci were isolated are indicated in black.

The stippled area in fig 3A indicates days in which nasal carriage is presumed.

ystematically, but swabs were taken from the rectal and mbilical areas of a number of babies on the tenth day. Of 29 abies swabbed in ward A only 2 isolations were made from ectal swabs, while the control ward B gave 14 positives out f 25. Of 29 umbilical swabs in ward A, 6 were positive, while n the control ward there were 11 positives out of 26.

Effect on occurrence of staphylococcal lesions.—During six months of spraying 4·0 g. a day a total of 340 babies were born in the unit, approximately equally divided between wards A and B. Altogether there were 14 minor lesions, mostly sticky eyes and pimples from which *Staph pyogenes* was isolated. None of these were isolated from the babies exposed to the drug by spraying, although the babies in both wards were looked after by the same nurses.

Nasal carriage in mothers and nurses.—58 nasal swabs were taken from the mothers on the first day in ward A, but not necessarily before they were exposed to the drug. Of these, 11 yielded *Staph pyogenes*, of whom, after five days' exposure, only 1 still gave a positive isolation. Nasal swabs from nurses on the unit failed to reveal the carriage of staphylococci resistant to BRL 1241.

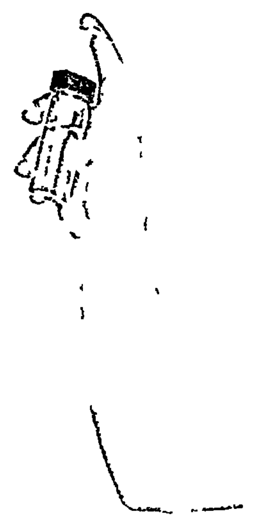


Fig 4—The spray in use.

Hypersensitivity to the drug.—No hypersensitivity phenomena were observed in the babies, mothers, or nurses.

Examination of dust.—(A) After six months' spraying the dust in ward A was found to have an inhibitory activity corresponding to 200 µg. of BRL 1241 per g. (B) The number of staphylococci in the dust of both wards was estimated by culturing serial dilutions of dust suspensions in salt meat broth (Maitland and Martyn 1948). By this method approximately 20,000 pyogenic staphylococci per g. were found in ward B, whereas none were demonstrated in the dust from ward A.

Air Sampling

Samples of air were taken after spraying 1·0 g. of BRL 1241 into ward A. 15 c. ft. of air sampled in the first fifteen minutes by means of a Bourdillon slit sampler was found to contain about 50 µg. of the antibiotic. Over the next two hours, however, similar samples showed only small amounts, in the form of occasional particles containing a few micrograms each.

Discussion

BRL 1241 seems to meet all the requirements for a drug to be used for spraying. It is highly bacteriostatic and bactericidal to *Staph pyogenes*, and, as it is stable in the dry form, the droplet nuclei probably retain activity. Six months' continuous spraying resulted in no untoward side-effects such as irritation of mucous membranes or hypersensitivity. No strains of pyogenic staphylococci naturally resistant to it were encountered, nor did resistant strains appear during the period of spraying.

The most important theoretical objection to this use of the antibiotic is the possibility of selecting drug-resistant mutants, thereby eventually interfering with its therapeutic use. The attempt to obtain resistant mutants on " gradient plates " (described above) constitutes a stringent test, and failure to obtain resistant strains in this way is of evidential value. Though we cannot say that the emergence of BRL 1241-resistant staphylococci is impossible, we think it highly unlikely. The new drug is based on the active portion of penicillin, and resistance to it would be expected to develop by mechanisms similar to those operating in regard to penicillin. These are of two kinds, of which only one is clinically important. In clinical lesions, the resistance of staphylococci to penicillin is entirely due to formation of penicillinase. The prevalence of such penicillinase-producers is almost certainly due to the selection of strains already extant when penicillin was introduced for treatment. Increase by selection in this manner is improbable, since no BRL 1241-resistant strains were met either in our own or other large series investigated (Thompson et al. 1960, Stewart et al. 1960). The acquisition of penicillinase activity in vitro by a strain is difficult to demonstrate, and if it occurs at all in vivo must be exceedingly rare. BRL 1241 is resistant to staphylococcal penicillinase, and, since the new drug has a molecular configuration which probably does not occur naturally, the acquisition of an enzyme directed against it by a single mutational step, or even by a few steps, is accordingly remote.

The other mechanism of penicillin resistance is of no clinical importance whatsoever. It occurs when a strain is artificially maintained in vitro in concentrations of the drug higher than those to which it was initially sensitive Such strains lack penicillinase, are never isolated from lesions, and are deprived of virulence Variants of this kind, tolerant to BRL 1241, if they occurred at all, would similarly be expected to be devoid of virulence and so could not become established as human pathogens

The idea of dealing with the nasal reservoir is not novel The application of an antibiotic or antiseptic ointment to the nose, however, has both practical and theoretical disadvantages Being laborious and æsthetically objectionable, it is often neglected More important is the fact that it may not reach the "business area" where staphylococci thrive After spraying, the droplet nuclei circulate in air and dust in the same way as staphylococci and reach the same places Thus with only a few minutes' spraying daily it is possible to achieve a circulation of the drug which reaches the breeding ground of staphylococci Furthermore, this method includes everyone in the environment

The results of spraying in the maternity unit leave no room for doubt that the colonisation of babies' noses can be prevented by this means It is well known that infants usually leave hospital carrying the prevalent "hospital staphylococcus" which shows multiple antibiotic resistance Such organisms may then cause breast abscesses in the mother and other infections in the home The prevention of this alone would justify the new technique Of wider import, however, is the fact that it proves the hypothesis that the epidemic cycle can be broken in this manner

A progressive effect was shown at first there was only a reduction in nasal carriage, but in the later stages there were practically no *Staph pyogenes* to be found This apparently cumulative effect of spraying may be due to three factors

1 There may be a continuous build-up of active BRL 1241 particles in the environment since the drug is stable in the dry form

2 There is a progressive reduction in nasal excretion of staphylococci by the infants, shown by a fall in the number of positive swabs and also by the growth of fewer colonies from those which were positive This necessarily leads to a decrease in the supply of staphylococci and therefore to the reversal of the vicious cycle. It is noteworthy that the time-honoured stratagem of closing a ward in the face of widespread sepsis operates in exactly the same way

3 The elimination of coagulase-positive staphylococci by BRL 1241 allows the establishment of other more resistant micrococci in the nose This flora may conceivably play a part in keeping out *Staph pyogenes* by antibiosis If this were so, the colonisation of noses with a population of resistant non-pathogenic micrococci may be a definite advantage

Which of these factors is most important cannot yet be said

We do not wish to suggest that the method of spraying employed, though a simple one, is the most economical or the best adapted for the purpose Variation in the amount of the drug, in relation to space, frequency of spraying, and the correct degree of nebulisation, awaits further study It may be that the dissemination of the drug as a fine powder will be best

We believe that staphylococcal cross-infection in hospitals can be best countered by breaking the epidemic cycle at its most vital point—the nasal reservoir—and removing the infective source by isolation and treatment of cases Our findings make it clear that prevention of colonisation of infants by *Staph pyogenes* is possible The ultimate aim is to abolish existing colonisation in the noses of adults Our limited observations on the moth suggest that this, too, is possible The problem nee further study as to dosage and conditions of administra tion In presenting these findings, our aim is to stimul such research

Summary

Staphylococcal cross-infection in hospitals is the res of a cycle in which the major source of the organisms is th nasal reservoir of the personnel and patients From th site of multiplication, staphylococci are voided into the a and dust, whence they colonise fresh noses Clinical sep is but an accident within the cycle

Spraying BRL 1241 into the air by a simple method w shown to prevent the usual acquisition of pyogen staphylococci by newborn infants

Spraying produces droplet nuclei of the drug, whi circulate in the air in the same way as staphylococci Th it is possible to break the cycle by physiological means its focal point—the nasal reservoir The properties BRL 1241 seem to render it the ideal drug for this purpos

The new method is economical in labour and material and is recommended as a basis for further research int the prevention of staphylococcal cross-infection

We should like to thank the medical and nursing staff of t maternity department at St George's Hospital for their ki cooperation in this work Our thanks are also due to the Beech Research Laboratories for letting us have a supply of the drug f this trial

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RENAL TRANSPLANTATION BETWEEN IDENTICAL TWINS

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THE first successful renal transplantation betwee identical twins was performed in 1954 by Merrill et a (1956) at the Peter Bent Brigham Hospital, and since th time a total of eight such operations have been reported b the same group (Murray et al 1958) The present report is concerned with another such transplantation performed at the Royal Victoria Hospital, Montreal, in May, 1958, and includes details of the immediate preoperative period and the first postoperative year The recipient twin was managed on a metabolic-balance regimen in the early postoperative period and some of the studies of this period will be published separately (Dossetor et al 1960)

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Case-report

PREOPERATIVE PERIOD

The patient was a 15-year-old white girl who was admitted on March 31, 1958, as an emergency to the Montreal Neurological Institute because of the sudden onset of epileptiform seizures associated with hypertension She had been in apparent health until the morning of admission She had noticed some heaviness of the head on wakening that morning, and the first seizure occurred several hours later Further seizures precipitated status epilepticus Inquiry into her previous health revealed that at the age of 4 years she had had an urinary infection which had been treated for several days with penicillin and which had given no further symptoms During the months prior to admission there had been no headache, no shortness of breath on exertion, no dysuria, and no polyuria or nocturia She had been admitted to a hospital three years previously for tonsillectomy, and examination of the urine at that time was reported as normal

On examination at the time of admission she was unconscious from the effects of the seizures as well as intravenous barbiturate. The abnormal findings were bilateral papilledœma and hypertension of 185/140 mm. Hg There was no evidence of localised neurological disease The fact that her hypertension might be secondary to renal disease was suggested by a " three-plus " proteinuria, and the urinary sediment contained one to two white blood-cells per high-power field and a number of hyaline casts containing granules, as well as rare mixed epithelial and white-blood-cell casts She was immediately given 2 5 mg reserpine intramuscularly to control the blood-pressure The serum level of non-protein nitrogen at this time was 82 mg per 100 ml.

The patient was fully conscious within 36 hours and her blood pressure had been controlled. There were no residual neurological signs The urine on culture had grown pseudomonas organisms, and bilateral pyelonephritis with hypertension was diagnosed As she had an identical twin sister steps were taken to explore the possibility of a renal-transplant operation should the return of renal function, after treatment of the urinary infection, not be adequate These steps were as follows (*a*) to investigate further the patient's disease, (*b*) to establish that the potential donor twin had a normal urinary tract, (*c*) to obtain as much proof as possible that the two twins were genetically identical, (*d*) to obtain legal authorisation for the operation, and (*e*) to control the management of the potential recipient during the preoperative period.

Investigation of Recipient Twin

Within 3 days of the start of antibiotic therapy for the urinary infection the urine became sterile, and it remained sterile thereafter However, as fig 1 shows, the serum-non-protein-nitrogen rose to 175 mg per 100 ml during the 1st week and, even after control of the infection, the level did not fall below 60 mg per 100 ml The hæmoglobin on admission was 86%, the white blood-cell count was 11,200 per c mm , the electrocardiogram was suggestive of left ventricular hypertrophy, chest X-ray showed normal cardiac contour, clear lung fields, serum electrophoretic pattern showed slightly lowered albumin, plain X-ray of abdomen showed small kidneys, and a retrograde pyelogram showed no obstructive element Cystoscopic examination revealed a normal lower urinary tract. Endogenous-creatinine clearance measured on two 24-hour samples gave the figures of 5 ml per minute on each occasion, and open renal biopsy showed chronic pyelonephritis to be present

Examination of Donor Twin

The urinalysis of the donor twin was normal, and her endogenous-creatinine clearance was 102 ml per minute Intravenous pyelography was normal, hæmoglobin was 90%, and on physical examination no abnormality was found.

The Proof of Identity

This was undertaken by Dr F Clarke Fraser and Dr J D Metrakos, of the Department of Genetics, McGill University The examination showed that, as well as appearing to be identical, the twins had similar dermatoglyphic patterns on all fingers and toes and the ridge counts were similar Comparison of blood-groups showed them to be identical, these results being confirmed by Dr Levine of the Ortho Laboratories, Raritan, New Jersey The conclusion was that the twins were monozygotic Skin-grafting was performed between the two twins by Dr M A Entin, and both grafts took successfully The graft on to the donor twin was biopsied four weeks later and no evidence of necrosis was found.

Authorisation for Operation

An operation on a healthy person representing a " mutilation " procedure is not covered by existing legislation, and special permission had to be obtained This consisted of a family council convened before a lawyer with affidavits from the surgeon and the donor twin A petition was then submitted to the Associate Chief Justice of the Province of Quebec who confirmed the family council's resolution

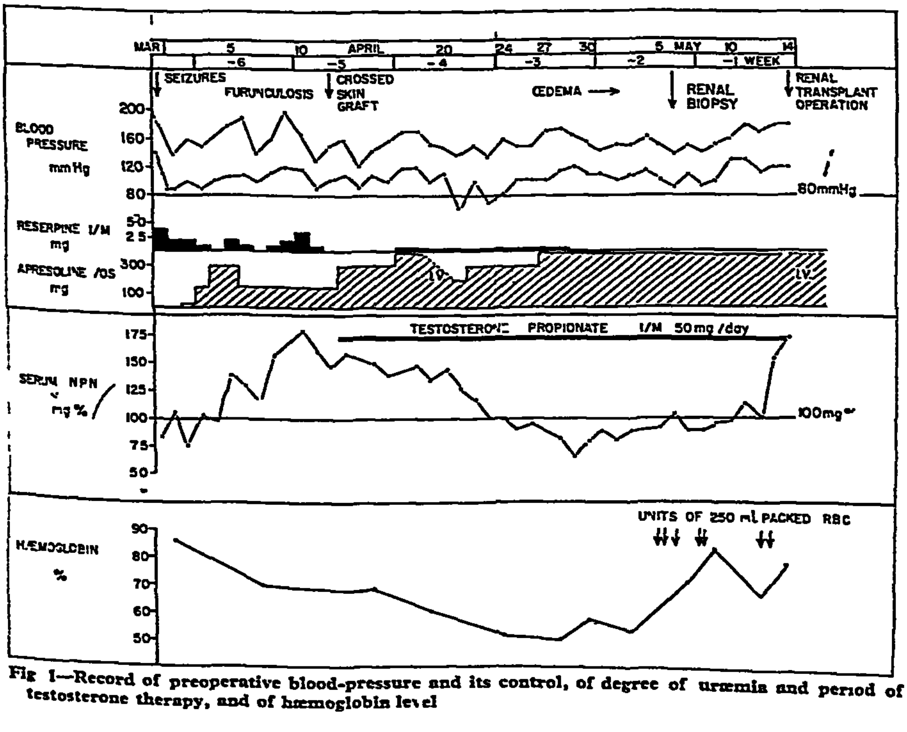

Fig 1—Record of preoperative blood-pressure and its control, of degree of uræmia and period of testosterone therapy, and of hæmoglobin level

Preoperative Management of Recipient Twin

The preoperative 6$^1/_2$-week period is outlined in fig 1 The blood-pressure was brought under control initially with intramuscular reserpine, and thereafter a combination of intramuscular reserpine and oral hydrallazine was used. At times the patient could not take oral preparations and the hydrallazine was given intravenously It can be seen that despite these measures the blood-pressure was not brought down to normal levels and the diastolic pressure remained at approximately 100 mm Hg during most of the preoperative period Despite the control of the urinary infection within 3 days, the serum level of non-protein nitrogen rose in the 1st week and thereafter fell slowly At the peak of the rise in serum-non-protein-nitrogen testosterone propionate 50 mg daily intramuscularly was begun, to retard the rate of endogenous protein catabolism (Kenyon et al 1940, Masson et al 1949) In addition to this, the protein intake was progressively reduced There was no protein in the diet in the few days before the operation However, it can be seen that the non-protein-nitrogen level of just under 100 mg per 100 ml was not maintained during the last 2 preoperative days when a rapid rise occurred for reasons that are not clear The patient's hæmoglobin was 85% on admission, but she became more anæmic and had to be transfused with a total of 7 units of 250 ml of packed red cells in the 10 days before the transplantation operation

During the early preoperative weeks it seemed that electrolyte balance could be achieved without a specifically controlled diet, though moderate sodium restriction was enforced For this reason all dietary restriction of electrolyte intake was removed in the 4th preoperative week The patient selected a diet that was high in sodium and chloride, and by the middle to the 3rd preoperative week she had become œdematous in the thighs, lumbosacral region, and periorbitally There was a 7 lb rise in weight to 99 lb The urinary excretion of sodium was found to have fallen to very low levels (less than 5 mEq per day) so the patient was placed on a rigid salt restriction

The reason for the low sodium output did not seem to be a reduced filtered load of sodium as the blood-pressure was not significantly lower during this time, nor was there a rise in the values of serum-non-protein-nitrogen In fact, as can be seen in fig 1, the serum-non-protein-nitrogen level fell during the first 2 weeks of testosterone therapy, the decrease was due, in all probability, to the anticatabolic effect of the hormone besides, to a lesser degree, the dilutional effect of the excess extracellular fluid

It seems that testosterone also caused the sodium retention Kenyon et al (1940) demonstrated that testosterone could have this effect, and probably this tendency would be more pronounced in a subject who had a reduced filtration-rate due to renal disease Freedman and Spencer (1957), however, noticed no weight gain in ten uræmic subjects treated with testosterone, but sodium balance was not done

As the increased tendency to retain sodium seemed to be due to an increase in the tubular reabsorption it could, perhaps, be counteracted by a diuretic An organic mercurial diuretic was used Any further damage to the diseased kidney would not be important as the transplanted kidney would take over within a short time Natriuresis was caused by each mercurial injection With these injections and strict control of sodium intake (10 mEq per day), the œdema went and the weight was reduced to 93 lb by the time of operation

During the few days before the operation the patient was vomiting and was stuporose The blood-pressure became difficult to control and her condition was critical on the day of operation Dialysis was considered but was not performed as it was felt that she would tolerate surgery

OPERATION OF TRANSPLANTATION

This was done by two surgical teams in adjacent operating-rooms In one room the urological surgeon, Dr K J MacKinnon, exposed the left kidney of the donor twin by an incision below the twelfth rib and prepared the vessels for ligation at the appropriate moment The left ureter was mobilised as far as the pelvic brim While this was being done Dr J C Luke prepared the anastomotic site The abdominal wall was opened through a Gibson incision which was extended at its lower extremity across the midline above the symphysis pubis The peritoneum of the right iliac fossa was reflected upwards and medially The common iliac artery was identified, and the internal and external iliac arteries were dissected from surrounding tissues When it was established that there was only one renal artery supplying the donor kidney, the recipient's internal iliac artery was clamped and severed and its branches were ligated and divided The external iliac artery was the inguinal ligament It was found that rotation of the internal iliac artery posterior to the external iliac artery produced l angulation than anterior (lateral) rotation

The vessels were ligated close to the aorta and inferior vena cava, the ureter was divided, and the kidney was removed The kidney was not perfused, it was taken directly to the adjacent operating-room and placed in the right iliac fossa of the recipient and the vascular anastomosis was performed There were two renal veins draining the donor kidney These two veins were first anastomosed, end-to-side, to the common iliac vein and external iliac vein and then the artery was anastomosed, end-to-end, to the internal iliac artery When the tapes and clamps were removed the kidney showed an immediate and apparently complete vascularisation The period of total ischæmia of the kidney was 58 minutes

The ureterovesical anastomosis was then performed The bladder wall was opened through a vertical incision 1 in to the right of the midline and a point chosen for ureteral anastomosis 1½ in above and slightly lateral to the right ureteral orifice A muscular tunnel was fashioned through the right lower wall of the bladder beginning 2 in above the site chosen for anastomosis While this was being done there was visible peristalsis in the ureter of the donor kidney and already some excretion of urine had occurred The ureter was threaded through the muscular tunnel and, after removal of 3½ in of redundant donor ureter, the end was anastomosed to the mucosa of the bladder with 4 sutures of atraumatic chromic catgut When the ureteral anastomosis was completed a rapid osmotic diuresis occurred Before the bladder was closed a jet of urine, showing some peristaltic fluctuation, was seen to reach up to several inches from the base of the bladder Extrinsic denervation had not apparently altered the peristalsis of the ureter A small calibre polyethylene catheter was passed to the renal pelvis and brought through the cystostomy wound A no 24 Foley catheter was placed in the bladder cavity and the bladder closed around both catheters Drains were inserted in the prevesical space and the iliac fossa and the wound was then closed

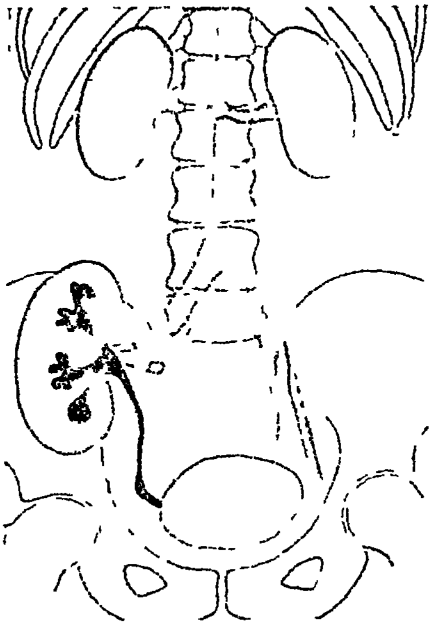

Fig 2—Diagram of site of renal transplantation

The entire operation took 3½ hours Both diseased kidneys in the recipient twin and their ureters were left in situ During the operation trichlorethylene, nitrous-oxide, and epidural anæsthesia were used The blood-pressure during the operation was stable at about 150/100 mm Hg

Fig 2 illustrates the end results, anatomically, of the operation

Heparin (750 international units) was given to the recip

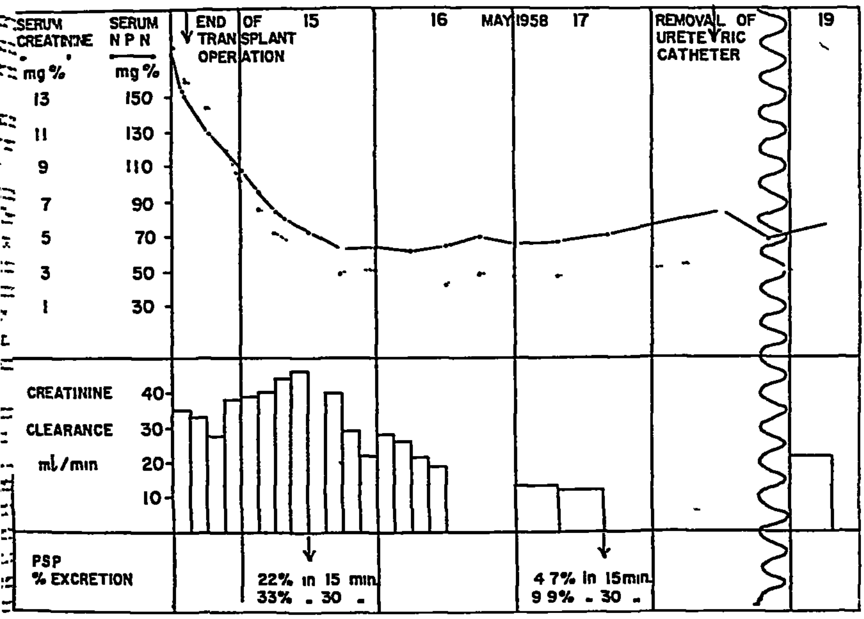

Fig 3—Rate of fall of serum non-protein nitrogen and of serum creatinine during the first 4½ postoperative days, endogenous-creatinine clearance, and % excretion of phenolsulphonephthalein.

twin approximately one hour before the anastomosis was begun, but no further anticoagulant was given. Towards the end of the operation the recipient twin passed a melæna stool of approximately 300 ml. The donor twin was not heparinized.

THE POSTOPERATIVE PERIOD

A rotation of three special nurses had been previously arranged. The patient's room had had all drapes and blinds removed—the room and all equipment had been thoroughly cleaned with 'Lysol' solution. Strict operating-room technique was used to minimise the risk of infection (Harris and Dossetor 1959).

Gastric drainage was maintained postoperatively, and all calories and electrolytes were administered intravenously through a caval catheter for 6 days. Thereafter the patient took food by mouth and supplemental parenteral therapy was given.

Tetracycline and penicillin were given intravenously—tetracycline 1 g. a day, penicillin 3 million units a day, for the first 2 weeks. Thereafter the patient was given sulphamethoxypyridazine 500 mg. a day, for 4 weeks.

The blood-pressure immediately after operation was 120/80 mm. Hg. From the 3rd to the 5th day the blood-pressure gradually rose to 155/100 mm. Hg mean value. The patient was then restarted on reserpine 0·25 mg. three times a day. Within another 5 days the mean blood-pressure was 140/90, and it continued around this range for another 3 weeks. Thereafter reserpine was discontinued, and the mean pressure during the latter part of her stay in hospital was around 120/90 mm. Hg.

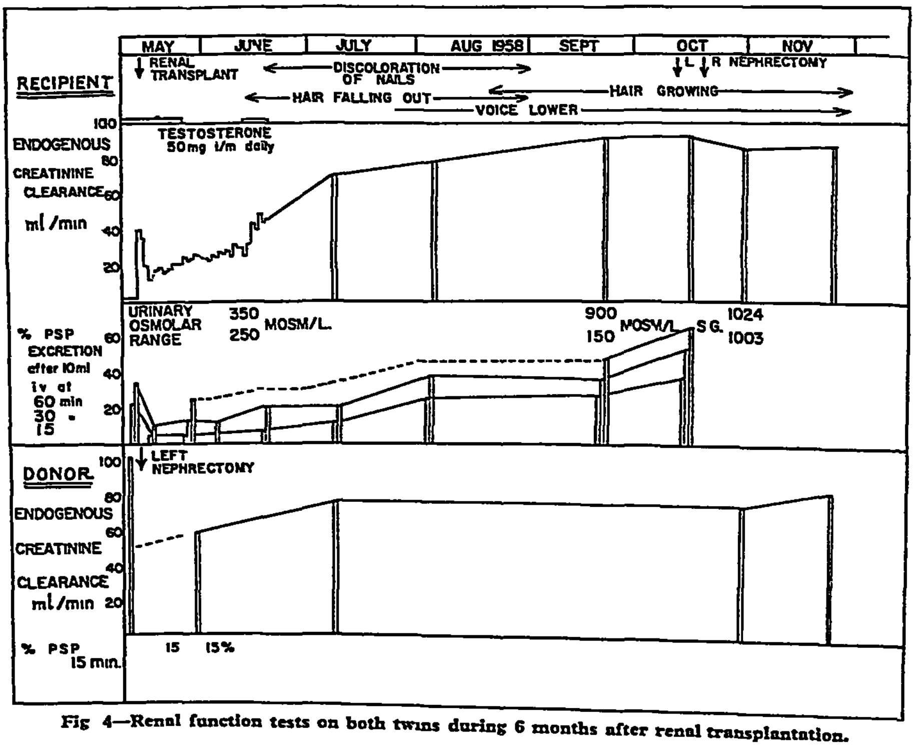

Fig 4—Renal function tests on both twins during 6 months after renal transplantation.

At no time from the end of the renal transplant operation was the blood-pressure a cause for anxiety or energetic treatment.

Fig 3 shows the changes in the level of serum creatinine and non-protein nitrogen during the first 5 days with the changes in endogenous-creatinine clearance and the percentage excretion of phenolsulphonephthalein (P S P). It is evident that the serum levels of creatinine and non-protein nitrogen fell very fast during the first 24–36 hours, but thereafter these levels remained steady and in fact on the 4th day showed a tendency to rise. The presence of the polyethylene catheter might have been a mechanical factor hindering free drainage so this was removed. The glomerular filtration-rate had diminished from May 15 to 17, the decrease being delayed until about 24 hours after the end of operation itself. There was a similar decrease in the percentage of excretion of P S P.

A very pronounced osmotic diuresis occurred in the first 9 hours after the end of transplantation, with urine volumes of 800 ml., 500 ml., and 400 ml. in the first three 3-hour periods. With these high flow-rates there was increased loss of sodium and chloride. On the 2nd day, however, the urine volumes were approximately 200 ml. in each 3-hour period at first and then fell to less than 100 ml. in a 3-hour period. This pronounced fall in the 3-hourly urine volume coincided with the levelling off of serum creatinine and non-protein nitrogen. There was no response to a water load of 1000 ml. of 5% glucose and water. The fluid was retained with a 2 lb. gain in weight. An increase in urine volume with a slight increase in sodium and chloride excretion occurred in response to the osmotic effect of 300 ml. of 60% glucose. The plasma-bicarbonate level rose from 16 9 mEq per litre at its lowest to about 25 mEq per litre after the first $2^1/_2$ days The rate of excretion of potassium in the phase of osmotic diuresis was not excessive and was only slightly greater than the 3-hourly loss of potassium during the subsequent days Rapoport et al (1949) reported that excretion of potassium does not increase in osmotic diuresis

The patient's condition improved rapidly in the first 3 days after the operation Within 24 hours her stupor had gone and within 4 days she was alert and felt well The Foley catheter draining the bladder and the two diseased kidneys provided no urine at all but was irrigated 6-hourly with 1% neomycin solution The vena caval catheter was removed on the 4th day and the gastric tube was removed the next day She was hungry and was allowed oral feedings, which were gradually increased in caloric and protein content The balance of electrolyte intake was given by parenteral infusion

The catheters were removed on the 4th postoperative day and a Foley catheter was passed to the bladder

When the cystostomy sinus appeared to be healed the Foley catheter was removed and spontaneous voiding was anticipated However, only small amounts of bloodstained urine were passed On the following morning the rectal temperature was 104 2°F and there was considerable pain extending over the whole suprapubic area and up into the right flank It was thought that this represented either extravasation of urine from the bladder into the extravesical space or vesicoureteral reflux On reinserting the urethral catheter this discomfort and pain disappeared and the temperature returned to normal The white-blood-cell count at this time was 30,000 per c mm 4 days later the Foley catheter was clamped for 4 hours, and again tenderness developed in the hypogastrium and in the right lower quadrant and the temperature rose During the 4th postoperative week the catheter was again removed and the patient voided spontaneously without pain She was awakened every 3 hours at night and made to void to prevent accumulation of urine in the bladder By this time the patient was eating well and showing a rapid return to normal health, and she was allowed up, the degree of activity being increased each day

The hæmatological findings were as follows There was a reticulocyte count of less than 1% during the first $2^1/_2$ weeks By the end of the 3rd week the reticulocyte-count was 2 5% and subsequently it was 4% It remained raised during the remaining weeks in hospital At the time of discharge the hæmoglobin was 13 g per 100 ml (84%)

The donor twin's recovery from simple nephrectomy was quite uneventful

THE FOLLOW-UP PERIOD

At the time of discharge from hospital the recipient's urine was sterile on culture and the urinary sediment included white blood-cells only, with no casts She was discharged on oral prophylactic doses of antibiotic and was seen at lengthening intervals during the 6 months between the transplantation and the subsequent bilateral nephrectomy During this period several changes occurred

Changes in renal function, both in the 6-week postoperative period in hospital and in the subsequent 6-month follow-up period, are indicated in fig 4 The creatinine clearance increased gradually from the 3rd postoperative day until the time of discharge from hospital in mid-June These figures for endogenous-creatinine clearance are based on a single blood measurement of the serum-creatinine level and a total of 24-hour urinary creatinine excretion The subsequent creatinine clearances were based on two 1-hour clearance periods with blood drawn at the mid-point It can be seen that the creatinine clearance increased quite rapidly in the first 2 months after the operation and levelled off by the 4th month at a figure of about 90 ml per minute Function in the transplanted kidney increased considerably despite the depression of function in the 3 days after transplantation 4 months after operation the creatinine clearance for the single transplanted kidney was almost the same as that of the two kidneys in the normal donor twin prior to nephrectomy

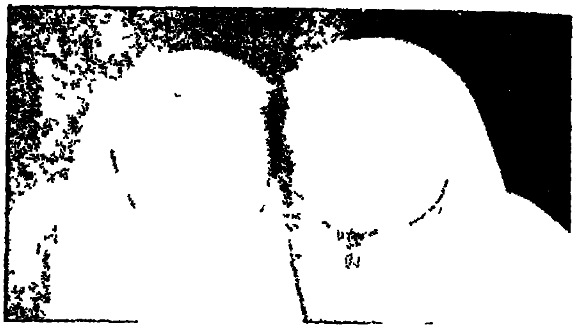

Fig 5—Pigmentation of the distal part of the two thumbnails 2 months after transplantation

Function in the remaining kidney of the donor twin als increased

The improvement in the 15-minute, 30-minute, and 60-minute percentage excretion of 10 ml of intravenous P.S.P (fig 4) parallels that of the creatinine clearance During th time in hospital the range of osmolality of the urine in th recipient twin was between 250 and 350 mOsm per litre 3 months later, the range of osmolality of the urine was from 150 to 900 mOsm per litre—approximately equivalent to a specific gravity range of 1003 to 1024 In February, 1960, the recipient twin's creatinine clearance was 83 ml per minute, and the donor twin's was 85 ml per minute Both urine sediments were normal and cultures were sterile

Several other changes in the recipient twin were noticed during this period between the two operations Shortly after she was discharged from hospital she noticed that her hair was falling out This began with a bitemporal recession of the hair-line and then thinning at the vertex, and subsequently practically all the hair fell out About the same time it was noticed that her voice was noticeably lower Although the falling hair could have been due, non-specifically, to the seriousness of her illness the lowering of her voice must have been due to the prolonged testosterone therapy Menstrual periods did not return for 3 months after the operation, by which time the hair was growing back However, the voice remains lower than that of her twin sister

Another feature of interest was that the distal half of her fingernails and toenails was noticeably darker than the mo

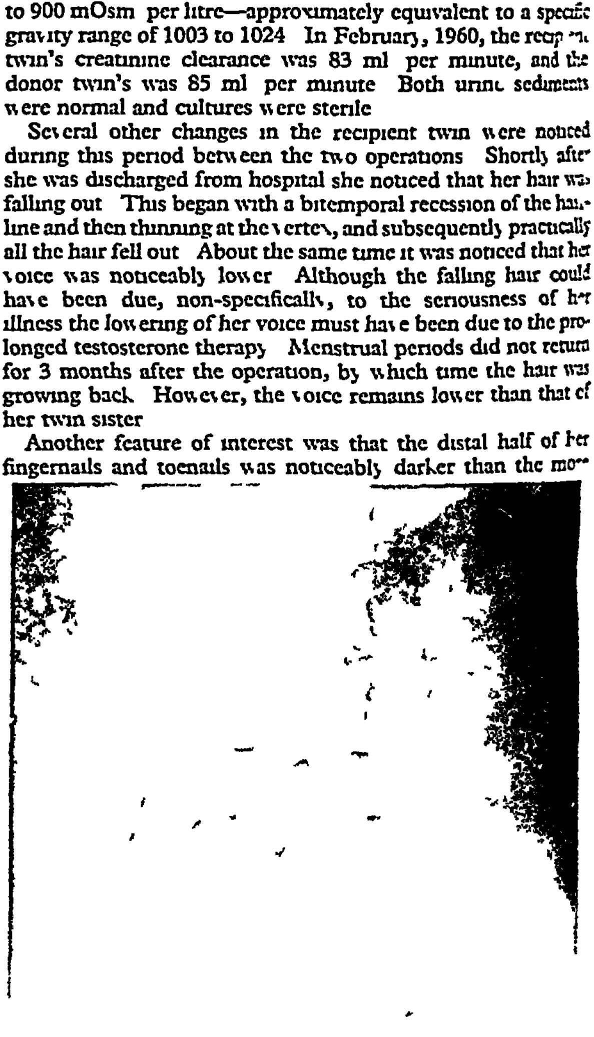

Fig 6—Intravenous pyelogram 6 weeks after transplantation

[illegible] part, the more proximal part was the normal colour (fig 5) This pigmentation probably represents the urochrome pigments that are known to be retained within the body in uræmia and which became incorporated into the substance of the nails The patient was not thought to have been pigmented before operation

5 months after operation the recipient twin was readmitted for bilateral nephrectomy This was performed by Dr K J McKinnon in two operations 1 week apart, and these were uneventful The blood-pressure which had remained slightly raised after transplantation regressed to normal (110/75 mm Hg) and has remained normal. The urine sediment subsequently has included epithelial cells but no white blood cells or casts Fig 6 shows a postero-anterior radiograph of the abdomen 5 minutes after intravenous injection of dye. No dilatation was present Additional studies revealed no evidence of vesicoureteral reflux Pathological examination of the diseased kidneys confirmed that they were both contracted by chronic pyelonephritis (weighing 38 g and 42 g)

Discussion

The group at the Peter Bent Brigham Hospital have suggested that the prognosis for the transplanted kidney is considerably worse if the original disease is glomerulonephritis rather than pyelonephritis

In two of their five recipient patients with glomerulonephritis, glomerulonephritis subsequently developed in the transplanted kidney To avoid this, in a later patient, they did a nephrectomy 2 days before transplantation and removed the other diseased kidney at the time of transplantation (Murray et al. 1958)

In the present case open biopsy showed that the disease was pyelonephritis Two diseased kidneys were therefore left in situ until the patient's health had improved 5 months later

The transplanted kidney was not cooled, perfused, or subjected to anticoagulation We considered that the delay and the intimal trauma with subsequent tendency to thrombosis that may be associated with manipulation of the kidney would decrease the chances of survival

The kidney in this case had two renal veins and one renal artery One of the two renal veins was short but wide and carried quite a large proportion of venous return, and yet vascular anastomosis was complete in 58 minutes Clearly such a period of ischæmia does not preclude subsequent functional improvement, and, indeed, renal "hypertrophy" has seemingly been as great as that which occurs in a normal kidney remaining after nephrectomy The mechanism of the delayed decrease in function is not known It was thought at the time that one of the renal veins had thrombosed, but this now seems very unlikely The change was probably due to a delayed secondary effect of ischæmia

The behaviour of the hypertension in this patient after transplantation and, later, after bilateral nephrectomy was similar to that observed by Merrill (Merrill et al 1956, Murray et al 1958) The partial control of severe hypertension by the transplantation of undiseased kidney-tissue is best explained by the renoprival theory of Grollman et al (1949) and Fasciolo's concept of the protective function of the normal kidney (see Braun Menendez 1958) Kolff (1958) has described a similar reduction in pressure in experimental renoprival hypertension in dogs after renal transplantation It is not possible to say whether the antihypertensive effect of relatively normal kidney tissue is due to (*a*) the neutralisation of renin or angiotensin, or (*b*) the partial neutralisation of a humoral (but not necessarily vasoconstrictive) substance produced by an ischæmic kidney that tends to prevent normal maintenance of blood-pressure by normal kidney tissue (see Floyer 1957), or (*c*) the neutralisation of extrarenal hypertensive substances The fact remains that malignant hypertension became mild after transplantation and disappeared after subsequent bilateral nephrectomy It is probably significant that the blood-pressure rose on the 3rd to 10th post-transplantation days when the delayed depression of renal function occurred

The administration of testosterone propionate in this case was probably the cause of considerable sodium retention preoperatively and also of voice changes and possibly changes in the hair subsequent to operation It is also probable that without the testosterone the preoperative uræmic state would have progressed more rapidly In addition the hormone may promote and accelerate renal "hypertrophy" (Lattimer 1942, McKay 1940)

Summary

Renal transplantation was carried out between two identical twins The recipient twin had bilateral chronic pyelonephritis

The operation was completely successful despite an apparent decrease in function of the transplanted kidney shortly after the operation The initially severe hypertension was very much improved after transplantation, and the blood-pressure reverted to normal after both diseased kidneys had been subsequently removed

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THE USE OF
NORETHANDROLONE IN ACUTE RENAL FAILURE FROM OBSTETRIC CAUSES

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THE GENERAL INFIRMARY AT LEEDS

TESTOSTERONE is known to prolong the survival of nephrectomised rats because of its "protein sparing" activity (Masson et al 1949) It has, therefore, been used in the treatment of acute renal failure, with variable but limited success (Derot and Bernier 1950, Freedman and Spencer 1957) Merrill (1955) states that "testosterone propionate is a definite, but not all important, adjuvant to treatment" in acute renal failure, and he notes that the protein-sparing effect "wears off" in 10–14 days In addition its virilising properties restrict its use in women

Now that new steroids with less androgenic activity, which still promote protein anabolism or antagonise protein catabolism, have been synthesised their use has been suggested in the management of patients with acute

TABLE I—CLINICAL DETAILS OF NINETEEN PATIENTS WITH ACUTE RENAL FAILURE AFTER PREGNANCY

Case no	Age (yr)	Diagnosis	Parity	Week of gestation	Toxæmia	Surgery	Re
1	27	Postpartum toxæmia	2	10	Postpartum only	0	Recove
2	39	Concealed accidental hæmorrhage	2	32	0	A R M *	"
3	38	" " "	3	32	+	A R M	"
4	27	Abortion and hysterectomy	6	16	0	Hysterectomy	"
5	21	Concealed accidental hæmorrhage	1	30	0	A R.M	"
6	27	Abortion	4	13	0	Evacuation of uterus	"
7	27	Eclampsia, pyelonephritis of right kidney, congenital cystic hypoplasia of left kidney	3	34	+	A.R M	Died
8	39	Concealed accidental hæmorrhage, cæsarean section	1	31	+	Cæsarean section	Recovered
9	30	Placenta prævia, cæsarean section and subtotal hysterectomy	4	34	0	Cæsarean section + subtotal hysterectomy	"
10	22	Concealed accidental hæmorrhage, cortical necrosis	1	32	+	A R M	Died
11	28	" " " " "	1	33	+	A R M	"
12	26	Pre-eclampsia with severe hepatitis	2	35	+	A.R M	Recovered
13	37	Concealed accidental hæmorrhage	1	30	0	A R M	"
14	36	" " "	5	31	+	A.R M	"
15	27	Concealed accidental hæmorrhage, cæsarean section, cortical necrosis	1	32	Pre-existing hypertension	Cæsarean section	Died
16	17	Concealed accidental hæmorrhage	1	34	Acute	A R M	Recovered
17	34	" " "	6	32	0	A R.M	"
18	13	Concealed accidental hæmorrhage, cortical necrosis	6	32	+	0	Died
19	22	Chronic pyelonephritis, concealed accidental hæmorrhage, cortical necrosis	1	30	0	0	"

*A R.M =artificial rupture of membranes

renal failure Norethandrolone, or 17 α-ethyl-17-hydroxy-19-nor-androst-4-en-3-one, is one such compound which in man has potent anabolic activity (Spencer et al 1957) and yet in laboratory animals is reported to be only 6% as androgenic as testosterone (Saunders and Drill 1957, 1958) In a preliminary communication in 1958 McCracken and Parsons described the effects of norethandrolone in patients with acute renal failure This compound depressed considerably the rate of urea formation in six patients with acute renal failure due to obstetric causes, and its effect was similar but less in three of five patients with acute renal failure unassociated with pregnancy Boen (1959) has commented that, although the results were encouraging, definite conclusions could not be drawn because the number of cases was small

We have now investigated in detail nineteen obstetric patients with acute renal failure (including those already reported) In sixteen of these the action of norethandrolone, testosterone, methyl testosterone, or progesterone was observed, the other three acting as controls

The Investigation

The Patients

Table I shows details of the nineteen patients studied and their diagnoses All developed acute renal failure following complications of pregnancy, and they were transferred to the General Infirmary at Leeds because they might require hæmodialysis As infection is known to increase the rate of protein catabolism no infected patient was chosen for investigation

Conditions of Study

From the time of admission all patients were given by mouth a standard daily regime of glucose 100 g and vitamins in 400 ml of water This achieved a daily weight-loss of 300–400 g Sensible loss of water was replaced as it occurred

A modified Kolff-Brigham rotating-coil artificial kidney was used for hæmodialysis, the indications being those of Parsons and McCracken (1959)

The three control patients (table I, cases 1–3) did not have steroids, whilst the remaining sixteen (cases 4–19), after a preliminary control period of 3–5 days, were given a course of the steroid under investigation, for 1–5 days In some patients a further course of one or more of these steroids was given over the next few days The drugs were given by mouth or by injection, in divided doses throughout the day

Protein catabolism was estimated by calculation of the 24-hour urea production Urine was collected in 24-hour periods from 9 A M , and blood was taken for analysis between 9 A M and 10 A M. each day Urea in plasma and urine was estimated by the method of Archibald (1945) Fæces were not collected, as the fæcal loss of nitrogen is relatively constant and independent of intake (Dempsey et al 1958) Lochia was not analysed because the investigations were made during the later puerperium The daily urea production was obtained from the sum of the daily accumulation of urea in the total body-water and the daily excretion of urea in the urine if this was formed The accumulation in the total body-water was calculated by multiplying the daily rise in the plasma urea level by the patient's total body-water, assumed to be 60% of the patient's weight as recorded at the start of the investigation. Any error in calculating the total body-water by this means will be constant for each patient and will not affect the result significantly Furthermore, as the total body-water was decreasing day by day, any reduction in urea production resulting from steroid therapy would be greater than that calculated

Results

Controls

Fig 1 shows the results in a patient (case 2) who had oliguria for 23 days The rate of rise of plasma-urea remained relatively constant throughout this period Similar results were obtained in the other two control patients (cases 1 and 3)

Effect of Norethandrolone

Table II shows the mean daily rate of urea production in the nineteen patients during the control period Fourteen of these were later given norethandrolone, which resulted in an average depression of urea production of 70% In six patients

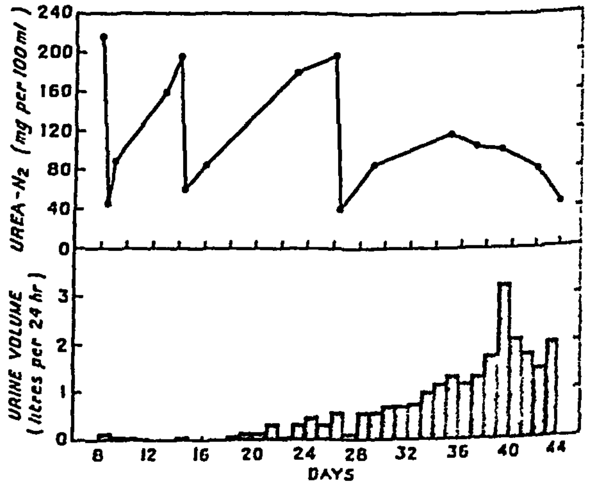

Fig 1—Daily plasma urea-N2 level and urine output in a control patient (case 2) not given steroids

TABLE II—EFFECT OF NORETHANDROLONE ON THE DAILY FORMATION OF UREA (AVERAGE OF 4–5 DAYS)

Case no	Control average daily urea production (in g N.)	Dose of norethandrolone (daily)	Average daily urea production with norethandrolone	% reduction in urea formation
1	5 3	0		
2	4 2	0		
3	7 2	0		
4	9 1	80 mg orally	1 8	81
5	6·4	80 mg orally	2 1	67
6	4 1	80 mg orally	0 2	95
7	8 4	100 mg. i.m *	4 1	51
8	6 3	100 mg i.m.	2 0	68
9	4 3	80 mg orally	1 9	56
10	5 5	0		
11	7 1	30 mg orally	2 6	63
12	8 0	30 mg. orally	3 6	55
13	8 7	30 mg orally	2 8	68
14	7·4	30 mg orally	3 0	59
15	9 5	30 mg orally	3 1	66
16	6 1	30 mg orally	1 2	80
17	8·0	50 mg i.m.	0 0	100
18	6·0	0		
19	7 2	30 mg orally	2 4	67

* i.m. = intramuscular

who had 80 or 100 mg of norethandrolone daily the average depression was 70%, and in seven patients who had 30 mg daily it was 65% In all cases there was a lag of about 24 hours before the full effect of norethandrolone was evident

Fig 2 shows the results in a patient (case 8) who was given 100 mg of norethandrolone daily by intramuscular injection after a control period of 3 days The rate of urea production was reduced from 6 3 to 2 0 g per day (68%) This reduction started suddenly 24 hours after norethandrolone was first given

Effect of Testosterone and Methyl Testosterone

Three patients (cases 10, 11, and 15) were given testosterone propionate 50 mg twice daily by injection, and one (case 16) was given methyl testosterone 50 mg 6-hourly by mouth The results are shown in table III In case 11 the urea production increased In the other three patients (cases 10, 15, and 16) the average depression of urea production was 37%, and in only one (case 10) did its effectiveness approach that of norethandrolone (fig 3) This patient seemed to "escape" from the effect about 3 days after testosterone was withdrawn Fig 4 shows the results in case 15 When testosterone propionate 50 mg was given twice daily by injection the rate of urea formation was reduced by 25%, but when norethandrolone 30 mg daily was given by mouth the reduction was increased to 66%

Effect of Progesterone

Two patients (cases 17 and 18) were given progesterone 100 mg twice daily by injection (table III) Urea production was depressed by 24% and 22% respectively The effect on case 18 is shown in fig 5

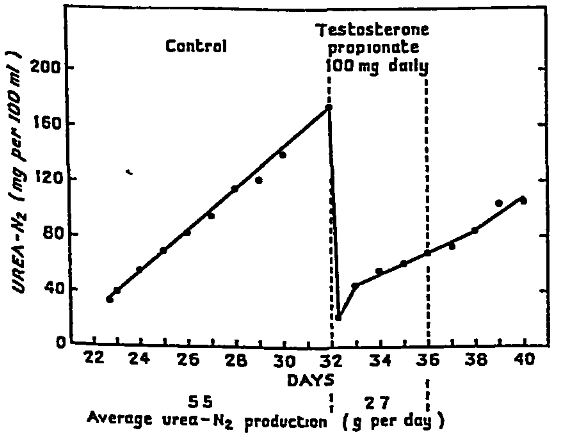

Fig 3—Effect of testosterone propionate on the rise of plasma urea-N, in case 10

Effect of Methyl Testosterone and Progesterone

This combination was studied in two patients (cases 16 and 18) who were given methyl testosterone 50 mg 6-hourly by mouth, and progesterone 100 mg twice daily by intramuscular injection The results are shown in table III Urea production was reduced by 64% and 66% respectively Figs 5 and 6 show the results in these patients Case 16 (fig 6) had 50 mg of methyl testosterone 6-hourly by mouth initially for 4 days, which decreased the urea production by 36% The same dose of methyl testosterone was continued for 4 more days together with 100 mg of progesterone twice daily by injection The rate of urea production decreased by a further 28% of the original rate After this she was given norethandrolone 30 mg daily by mouth This caused further reduction of urea production to 80%, but fig 6 shows a 48-hour time-lag before the effect of adding progesterone to methyl testosterone became apparent, and in actual fact a combination of methyl testosterone and progesterone seemed to be as effective as norethandrolone

Fig 5 shows the results in case 18 This patient had progesterone at first with a 22% reduction of urea production, but when methyl testosterone was added the reduction was increased to 66% The graph also shows the escape from the effect of steroids after 5 days

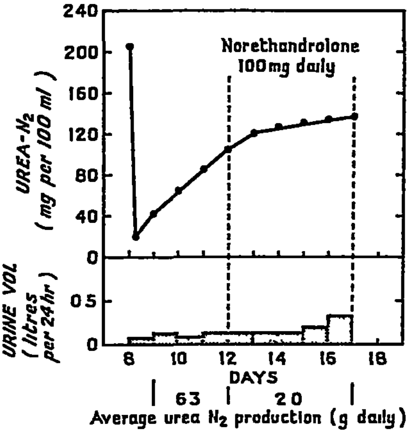

Fig 2—Effect of norethandrolone 100 mg by injection on the rise of plasma urea-N, in case 8

Thus, while progesterone causes a depression of urea production, and methyl testosterone has a somewhat greater effect, the two drugs together produce an effect similar to that of norethandrolone.

Side-effects of Norethandrolone

The two theoretically important side-effects of norethandrolone are virilisation and jaundice In addition to the fourteen cases studied above we have treated with norethandrolone eleven cases of acute renal failure from obstetric causes In none of these 25 patients has any side-effect been observed One patient (case 12) had severe toxæmia of

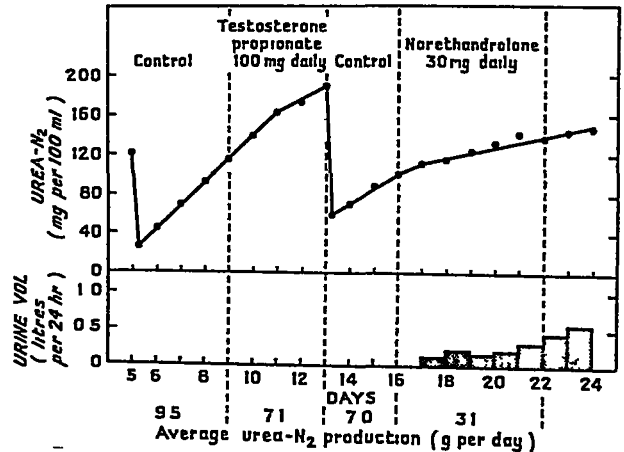

Fig 4—Comparison of the effects of testosterone propionate by injection and norethandrolone by mouth in case 15

TABLE III—THE EFFECT OF TESTOSTERONE, METHYL TESTOSTERONE, PROGESTERONE, OR A COMBINATION OF METHYL TESTOSTERONE AND PROGESTERONE ON THE DAILY FORMATION OF UREA (AVERAGE OF 4–5 DAYS)

Case no	Control average daily urea production (in g N_2)	Daily dose of testosterone	Average daily urea production on testosterone	% reduction in urea formation	Daily dose of progesterone	Average daily urea production on progesterone	% reduction in urea formation	Daily dose of methyl testosterone and progesterone	Average daily urea production on methyl testosterone and progesterone	% reduction in urea formation	Daily dose of norethandrolone	Average daily urea production on norethandrolone	% reduction in urea formation
10	5·5	Testosterone propionate 100 mg i m *	2·7	51									
11	7·1	Testosterone propionate 100 mg i m	10·3	−45							30 mg orally	2·6	63
15	9·5	Testosterone propionate 100 mg i m	7·1	25							30 mg orally	3·1	66
16	6·1	Methyl testosterone 200 mg orally	3·9	36				200 mg of each	2·2	64	30 mg orally	1·2	80
17	8·0				200 mg i.m	6·1	24				50 mg i m	0·0	100
18	6·0				200 mg i m	4·7	22	200 mg of each	2·0	66			

* i m = intramuscular

pregnancy with gross liver damage and signs of impending hepatic coma before treatment, but these changes subsided uneventfully during administration of norethandrolone

In cases of acute renal failure treatment with norethandrolone is unlikely to last longer than 3 weeks As both virilisation and jaundice take some time to develop we do not think that the use of norethandrolone in acute renal failure imposes a significant hazard

Duration of Effect

Figs 3 and 5 show an escape from the effects of testosterone and a combination of methyl testosterone and progesterone 3–5 days after treatment is stopped Similar results have been found with norethandrolone by Schedl et al (1959) in normal subjects We have not been able to demonstrate an escape after withdrawing norethandrolone The maximum effect, however, certainly lasted at least 2–3 days after norethandrolone was stopped but further observation was impossible, either because renal function was recovering or because the patient deteriorated and died—a previous percutaneous renal biopsy having confirmed the presence of complete cortical necrosis

Discussion

Incidence of Acute Renal Failure in Pregnancy

The commonest cause of acute renal failure in later pregnancy is concealed accidental hæmorrhage, which is said to occur in 0·5–0·6% of all deliveries (Sheehan and Moore 1952, Sexton et al 1950) Sheehan and Moore reported seventy-five deaths in 115,000 deliveries, of whom forty-four died of renal failure in the puerperium or died on the day of delivery, showing severe renal damage post mortem These patients (0·04%) probably represent those with complete cortical necrosis or other extensive renal damage, but anything up to half of the cases of concealed accidental hæmorrhage may have had some degree of renal impairment—an incidence of about 0·3% of deliveries

Less than 10% of these patients are likely to have complete cortical necrosis, and it is therefore important that life should be supported long enough to allow possible recovery of renal function As many patients with acute renal failure from concealed accidental hæmorrhage have not shown signs of recovering renal function for up to 3 weeks we have not performed diagnostic procedures, such as retrograde pyelography and percutaneous renal biopsy, until after this time had elapsed During the period of supportive management the use of norethandrolone has reduced the necessity for dialysis, and several cases have recovered without the use of the artificial kidney

In other conditions causing acute renal failure associated with pregnancy, such as hæmorrhage from placenta

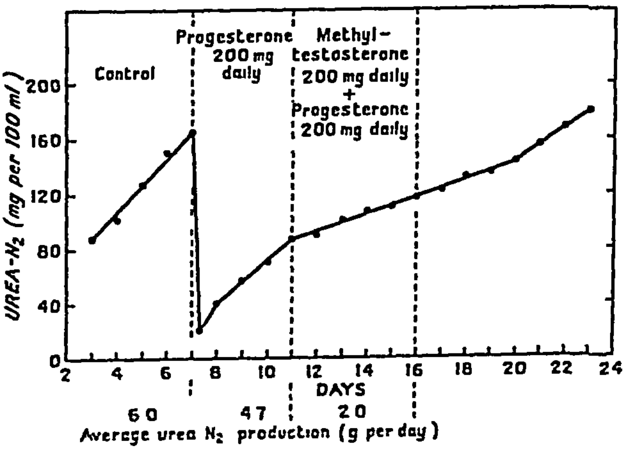

Fig 5—Effect of progesterone and of a combination of progesterone and methyl testosterone in case 18

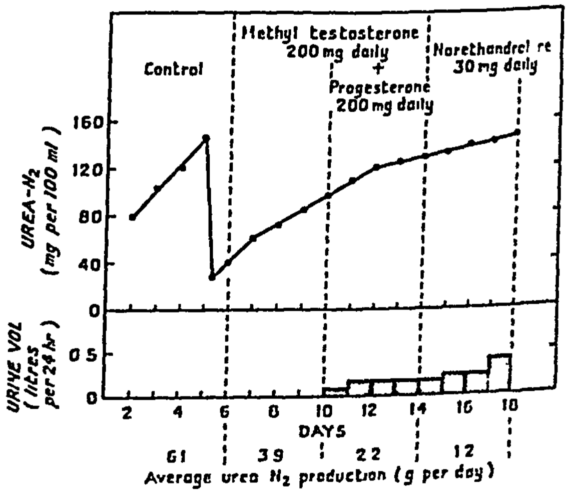

Fig 6—Effect of methyl testosterone of methyl testosterone and progesterone, and of norethandrolone in case 16

prævia and abortion, we have found norethandrolone equally effective

Reduction in Protein Catabolism

It is generally agreed that the symptoms of acute renal failure are due to accumulation of the products of protein breakdown. With a diet composed solely of carbohydrate, the rate of protein breakdown is said to be reduced to a minimum (Gamble 1947, Munro 1951) Urea is a convenient marker for the rate of protein breakdown, although its role in producing the clinical effects of uræmia is uncertain Factors other than diet affect the rate of protein breakdown, and in pregnancy the metabolism of protein appears to be modified

Poo et al (1940) showed in the rat that during pregnancy on an adequate protein intake the total quantity of body protein formed is higher than in normal rats on a similar diet, and that the largest proportion of this protein is laid down in the liver Venning et al (1959) have shown a negative nitrogen balance for at least 10 days after parturition In postpartum renal failure this will increase the rise of plasma-urea Thus any measure is of value which will reduce the rate of protein breakdown so that toxic levels are not reached before urine output is re-established The necessity for and frequency of hæmodialysis will consequently be reduced in the more severe cases, and more patients could be managed in hospitals where there are no facilities for hæmodialysis By reducing the need for starvation, it should lessen the morbidity and shorten the period of convalescence

In the fourteen cases which were given norethandrolone, the average reduction of protein breakdown was about 70% The effect on protein breakdown of norethandrolone 30 or 80 mg daily by mouth, or 50 or 100 mg by intramuscular injection, is of the same order For practical purposes 30 mg of norethandrolone by mouth or 50 mg by injection daily appears to achieve the greatest effect within 24 hours of first starting the drug, and the effects persist for several days after a course lasting 4–5 days We have not determined the optimum period of treatment In addition to the effect on protein breakdown the changes in other chemical indices of uræmia are slowed down to more or less the same degree

Norethandrolone is more effective than either methyl testosterone or progesterone alone, and at least as effective as a combination of these two drugs, but, perhaps of greater importance, it acts more quickly We therefore recommend that norethandrolone be used routinely in the management of acute renal failure associated with pregnancy

Mode of Action

The mechanism of action of norethandrolone is unknown There is no obvious correlation with the cause of renal failure except that it has more effect in patients with acute renal failure associated with pregnancy We have also seen a response in some patients with acute renal failure associated with nephritis, and in patients with traumatic uræmia, but this is often masked by the severe catabolic stresses of infection and other complications Gjørup and Thaysen (1958) too have found that patients with chronic renal failure respond to norethandrolone

The greater effect of norethandrolone in patients with renal failure associated with pregnancy is unlikely to be due to inhibition of uterine involution Two of our patients, who had hysterectomies performed at the onset of renal failure, still showed the typical response Whether the progestational effects of norethandrolone have any great bearing on its anticatabolic activity is uncertain In two patients progesterone appeared to have some anticatabolic activity, this contrasts with the findings of Landau et al (1958), who showed that progesterone, and other progestational compounds with a C_1- side-chain in the beta position, usually had a catabolic effect in non-pregnant women Possibly during the puerperium progesterone itself is anticatabolic, and the so-called anabolic steroids may be more effective in patients at this time

Summary

The effect of certain steroids on patients with acute renal failure after pregnancy has been studied

Norethandrolone can reduce the rate of urea production by up to 70% in these patients This is significantly more than the effect of either testosterone or progesterone alone, and is at least as great as the effect of a combination of these two drugs

The mechanism of action of the so-called anabolic steroids remains uncertain, but they may in fact be anticatabolic

It is suggested that norethandrolone be used routinely in the treatment of prolonged oliguria or anuria following pregnancy, because this will reduce the necessity for and frequency of hæmodialysis

We wish to thank Mrs S M Hobson, A M I L T, for the chemical estimations, and Messrs G D Searle & Co for supplies of ‘Nilevar’

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PASTEURELLA SEPTICA IN CHRONIC NASAL SINUSITIS

EILEEN O BARTLEY
M D Belf, D.P H

SENIOR LECTURER IN BACTERIOLOGY, QUEEN'S UNIVERSITY, BELFAST

IN 1945 a strain (AW) of *Pasteurella septica* was isolated from a farmer with frontal sinusitis (Bartley and Hunter 1947)

Case-record

This patient was first seen in 1943 when a right middle turbinectomy was performed, but because of persistent frontal headache and a greenish purulent nasal discharge a right radical external fronto-ethmoidal operation was done in 1945 combined with penicillin therapy At this operation no involvement of bone was noted The patient remained well until 1954, when he developed intermittent swelling round his right eye and a greenish right-sided nasal discharge These symptoms continued until 1958 when he was again referred to Mr Kennedy Hunter X-ray examination showed opacities of both antra and of the right frontal sinus, and blood and pus were found in the right antrum on exploratory puncture In January, 1959, a right external frontal operation showed extensive involvement of the bony septa between the sinuses and infection of the frontal and maxillary bones After operation the patient was discharged without symptoms, but when he was seen ten months later he was again complaining of swelling round his right eye suggesting the persistence of infection

Bacteriology

In January, 1959, a second strain (AW/59) of *Past pestis* was isolated from pus taken at operation Unfortunately the AW strain isolated in 1945 had not remained viable and it was impossible to make a direct comparison of the two strains They were, however, similar in morphological, cultural, and biochemical properties apart from a few minor differences for example, strain AW grew on MacConkey's medium while AW/59 did not, and the AW strain was sensitive to penicillin while the AW/59 strain was resistant The AW/59 strain was also resistant to sulphathiazole but sensitive to all other antibiotics against which it was tested

Using the criteria of Smith (1959) it is not possible to assign AW/59 to an animal source Thus capsules were present, colonies were not mucoid, hyaluronic acid was produced, iridescence was not seen, and acid agglutinability was present at pH 2 5 and 3 5 but not at pH 4 5 or 5 0 The organism was pathogenic for mice, and it produced fermentation of xylose and mannitol but not sorbitol, maltose, or trehalose

An agglutination test using immune rabbit sera was carried out as previously described (Bartley and Hunter 1947) with the following results

Strain	*Titre of rabbit antisera to AW/59 strain* *Unabsorbed*	 *Absorbed by AW/59 strain*	 *Absorbed by 1737 strain*
AW/59	1 1280	<1 5	1 80
Nat Type Cult no 1737	1 1280	1 80	1 80

It would appear, therefore, that AW/59 and the National Type culture strain no 1737 are serologically related but not identical A similar conclusion was reached when the AW strain was compared with 1737 in 1945

Blood taken from the patient in November, 1959, had an agglutination titre of 1 40 against the AW/59 strain In 1945 the patient's serum had no demonstrable antibody—which is not an unusual finding in *Past septica* infections

Discussion

Human infections with *Past septica* are uncommon, and the few reported cases of sinus infection with this organism appear to have run very chronic courses Hadorn (1938) recorded a case of *Past septica* meningitis eight months after a fracture of the skull involving a presumably infected right frontal sinus, and Bezjak and Mimica (1952) described a patient with *Past septica* sinus infection who had symptoms and a greenish nasal discharge for six years It is unfortunately impossible to exclude reinfection in the present case, but it seems equally reasonable to assume a chronic infection over a period of at least twelve years Apart from the change in penicillin sensitivity, the AW and AW/59 strains appear to be very similar

Summary

A strain of *Past septica* was isolated from a patient with frontal sinusitis in 1945 and again in 1959

Direct comparison of the two strains has not been possible, but they appear to be essentially similar except in certain biochemical properties and in penicillin sensitivity

Assuming that reinfection did not occur, *Past septica* sinusitis may apparently be very chronic and last for as long as fifteen years

I wish to thank Prof G W A Dick and Mr Kennedy Hunter for cooperation and help in the preparation of this paper, and Mr T Connor for technical assistance

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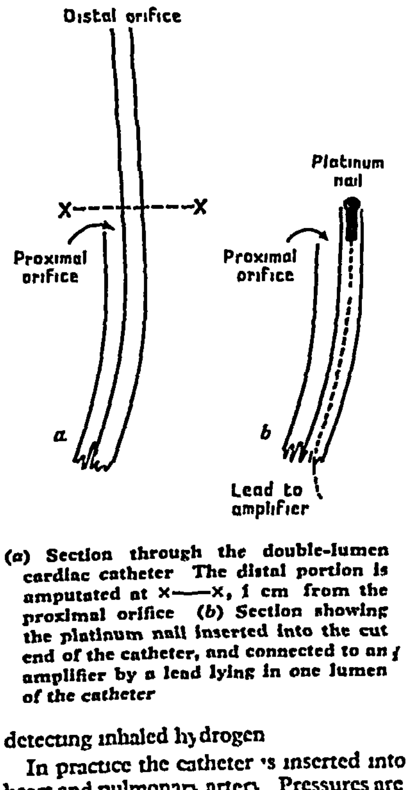
New Inventions

A MULTIPURPOSE CARDIAC CATHETER

The standard cardiac catheter has a lumen through which pressure pulses and blood samples may be obtained, and injections may be made For recording intracardiac electrocardiograms a catheter is necessary with an electrode near its tip When inhaled hydrogen is used to detect left-to-right intracardiac shunts a catheter bearing a platinum-black electrode is necessary [1] The investigation of patients with congenital heart-disease has been simplified by using a catheter capable of serving each of these purposes

The distal portion of a double-lumen catheter is amputated at X—X (see figure) A platinum nail, cemented into the cut end, is connected by a lead running through the lumen to a suitable amplifier The platinum nail is "blacked" by electrolysis The finished catheter thus bears at its tip the orifice of one lumen, and the platinum-black electrode The electrode may be used for recording the intracardiac electrocardiogram, or for detecting inhaled hydrogen



(a) Section through the double-lumen cardiac catheter The distal portion is amputated at X——X, 1 cm from the proximal orifice (b) Section showing the platinum nail inserted into the cut end of the catheter, and connected to an amplifier by a lead lying in one lumen of the catheter

In practice the catheter is inserted into the right side of the heart and pulmonary artery Pressures are recorded through the lumen Left-to-right shunts are detected and localised by hydrogen inhalation Right-to-left shunts are revealed by indicator-dilution curves after dye has been injected through the lumen of the catheter The intracardiac electrocardiogram is recorded when necessary

The catheter may be obtained from Messrs Chas F Thackray, 10, Park Street, Leeds, 1 We are indebted to Mr H Worrsch F I S T, of the department of physical chemistry in the University of Leeds, for overcoming the problem of providing a cardiac catheter with a platinum black electrode

H M S was in receipt of a grant from the Nuffield Foundation

P G F NIXON
M B Durh M R C P

H M SNOW
Technician

Department of Thoracic Surgery,
The General Infirmary at Leeds

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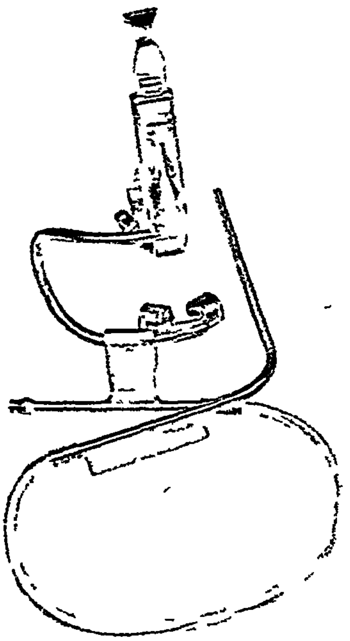
[1] Clark L C, Jr, Bargeron, L M, Jr *Surgery* 1959, 46 77

A SUCTION TUBE FOR USE DURING TONSILLECTOMY AND ADENOIDECTOMY

The suction tube designed by Sidney Yankauer (1872–1932) of New York, when he was laryngologist at Mount Sinai Hospital, was brought into use with the guillotine operation and the hurried adenoidectomy performed with the patient on his side.

Many surgeons, however, have now adopted dissection tonsillectomy preceded or followed by a more leisurely adenoidectomy.



Under direct vision the distal curve of the Yankauer instrument is unnecessary and obscures the view. A straight shaft is needed in order to apply the end to the point seen. The bulbous end is a safeguard if the instrument is used blindly, but is cumbersome when used during dissection.

The instrument is made with a light handle angled at 90°, to be held in the reverse grip of the left hand. The shaft is a straight tube with a round hole at each side $^{1}/_{4}$ in from the open extremity. This arrangement reduces the hissing heard when the sucker is in use. The handle end is connected by a 15 in. flexible plastic tube to an adaptor hanging by a flat hook from the arch of a Boyle-Davis gag. To the large end of this adaptor the usual pressure tube from the suction pump is attached. This hooked adaption prevents the instrument from falling to the floor if unattended.

Messrs Allen & Hanburys, Bethnal Green, London, E 2, have produced this suction tube in stainless steel with a transparent tube made by Portex Plastics. Mr G A Cook took the photograph.

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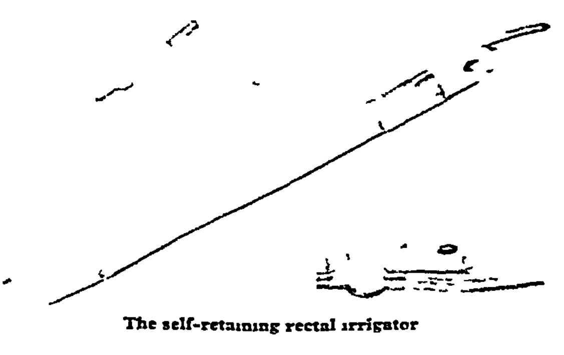
London, S.E 5

BRIAN PICKARD
M.B Lond, F R C S, D L.O

A RECTAL IRRIGATOR

Rectal irrigation with a 1 in 500 solution of mercuric perchloride, to destroy free carcinoma cells in the bowel lumen, during anterior resection for carcinoma is now well established.[1]

The usual method of irrigation is by means of a large-bore rubber tube or catheter introduced through a proctoscope when the bowel clamp is in place before the anastomosis. This procedure entails disturbing the towelling, and interrupting the operation to some extent. To avoid this disturbance, a self-retaining double-lumen rubber catheter has been found useful, and has the advantage that large quantities of the irrigating solution can easily be washed through the rectum. The physical removal of free carcinoma-cells complements their chemical destruction by the irrigating fluid.



The self-retaining rectal irrigator

The irrigator (see figure) comprises a stiff red rubber tube 14 in long, with a $^{1}/_{2}$ in lumen, and with two side-holes $^{1}/_{2}$ in long just behind the tip. The inlet catheter is $^{1}/_{4}$ in wide and projects 2 in. beyond the main tube. The self-retaining inflatable bag (see inset) of translucent rubber and 25 ml capacity is situated $1^{1}/_{2}$ in. behind the tip of the irrigator, and has a pilot bag. The whole instrument can be sterilised by boiling.

Before the operation begins the irrigator is inserted into the rectum, and the self-retaining bag is inflated. After the distal bowel clamp is in place, irrigation can proceed without interrupting the operation. The irrigating solution drains via the main tube into a suitable receptacle without contaminating the patient or the assistants.

The irrigator has been constructed by Messrs J G Franklin & Sons Ltd., 51, Manchester Street, Portman Square, London, W 1.

I am grateful to Mr E C Butler and Mr R P Warren for help and advice.

Poplar Hospital,
London, E.14

L. R. DE JODE
M.B Lond., F.R C.S

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[1] Goligher, J C., Dukes, C. E., Bussey, H R. *Brit J Surg* 1951, 39, 194

Reviews of Books

Coloured Immigrants in Britain

J A. G GRIFFITH, JUDITH HENDERSON, MARGARET USBORNE, DONALD WOOD London Oxford University Press, for the Institute of Race Relations 1960 Pp 225 25*s*

This useful book brings together much of the material written in recent years about coloured immigrants. It includes an analysis of the facts and figures known to local authorities and voluntary welfare organisations, a summary and assessment of the existing sociological work on the subject, a statement of the attitudes of the Government, the political parties, the trade unions, and other bodies, a discussion from the legal standpoint of the existing law and of measures, such as the restriction of immigration and deportation of undesirable persons, that have been proposed, and a summary of the experience of the United States in such matters as housing and employment.

Information was obtained from local-government and other officials by means of a long questionary, including specific questions on employment, housing, and health matters, and research-workers reported on visits to thirty-two centres of coloured population. It has been impossible to publish the summaries of statistical material and opinions, but the information is available for inspection in the Institute of Race Relations.

In the past ten years large numbers of West Indians, West Africans, Indians, and Pakistanis have immigrated to Britain, and in December, 1958, the coloured population from the Commonwealth was reported to be about 210,000. At the time of this survey economic conditions in the West Indies had improved and propaganda measures by West Indian Governments, explaining to prospective immigrants the difficulties of work and accommodation in Great Britain, seemed to have slowed the flow, but in the first six months of 1960 many West Indians were still arriving in this country. Immigrants from India and Pakistan come from rural areas and are separated from the white population in their home country by barriers of religion, language, and culture and show little desire to mix with the British people. Other migrant workers from Africa have come to this country as seamen in the past hundred years but have recently moved inland from the ports where they originally lived.

London has far the largest coloured population (90,000) but estimates of the population vary widely in all areas where coloured people have recently settled The other main centres of population were at the time of the survey said to be Birmingham (25,000–30,000), Liverpool and Manchester (8000–10,000), Nottingham (4000–5000) Most of the immigrants are men between 20 and 45 and only about 10% of the Indians and Pakistanis and 20–30% of the West Indians are women Mixed marriages are uncommon except in old-established coloured communities, but semi-permanent or temporary liaisons between coloured men and white women are not unusual, and white women, both married and unmarried, play a steadying and fostering part among recent arrivals Coloured children seem to meet no serious difficulties in the schools, although special classes have sometimes been organised for pupils handicapped by an imperfect knowledge of English But when coloured children leave school "they leave a cosy world where they are judged by their skill at games or the colour of their blazer and enter the adult world where the colour of their skin may be important"

The greatest problem facing the coloured immigrants is to find a home, and most of them live in poor working-class areas in large Victorian terrace houses that are dilapidated and unsatisfactory if not actually due for clearance Most coloured workers are in unskilled jobs and many are employed in very hot and humid conditions Others work as pedlars, in public transport, and in restaurants

Studies by Springett and others on the higher incidence of pulmonary tuberculosis in immigrants from Asia seem to be confirmed by the rather patchy statistics collected during the survey The findings of Willcox on the increased incidence of gonorrhœa amongst immigrants, especially West Indians, are noted The available evidence shows that very few coloured people, whatever their nationality, go into mental hospitals and the number who commit suicide is extremely small

Bibliography of Internal Medicine

Selected Diseases ARTHUR L BLOOMFIELD, M D, professor of medicine emeritus, Stanford University Chicago University of Chicago Press London Cambridge University Press 1960 Pp 312 48s

Professor Bloomfield, puzzled by the difficulty of arousing serious interest in the historical side of medicine, blames the conventional method of treating the subject, and the inaccessibility of the important papers To remedy this he published two years ago a selected bibliography of important contributions on communicable diseases, with extracts and critical comments In the present volume he applies the same technique to twenty-one diseases "of old and honourable lineage" He has tried to list every reference of fundamental importance in the development of each, with appropriate excerpts for the benefit of the reader who does not have access to the originals or who has difficulty with French or German The diseases are what one would expect, with the exceptions of chlorosis and trichinosis, and it is odd, since the volume is intended especially for students, that he plays down Paget's discovery of the parasite while he was a preclinical student at Barts Dealing with diabetes mellitus and subacute bacterial endocarditis, he abstracts at some length twenty-one and twelve important papers respectively with detailed references Like its predecessor this is a valuable source-book that is likely to stimulate further reading

Florence Nightingale's Nurses the Nightingale Training School

LUCY SEYMER London Pitman Medical Publishing Co 1960 Pp 169 20s

JUST a hundred years have gone by since the "Nightingale School" was opened, and the centenary has been appropriately marked by this account of its development The school had its origin in a public subscription raised in Florence Nightingale's honour in 1855 while she was working in the Crimea The fund eventually contained £44,000, and it is noteworthy that a fifth of this total was contributed from barracks, messes, and even the front line, by all ranks of the Army This money was used, under the direction of a small council nominated by Miss Nightingale herself, to train probationers at St Thomas's Hospital

Fifteen nurses initiated the scheme, and, though the size of the school increased, its eventual influence on nursing all over the world was not derived from the mere number of its pupils It sprang rather from a stipulation in the earliest days that the trainees might subsequently take posts only in approved hospitals—that is to say, ones in which they would be permitted to introduce the standards and methods of the parent institution itself

The Nightingale Training School may be a hundred years old, but it is interesting to note how many of its basic principles still endure as cornerstones of nursing today (These include the concept of a matron having absolute responsibility for the nursing staff the rendering of periodic reports by each sister on the student nurses in her ward, and the importance attached to all probationers living together, and in a home the better to learn order and discipline) Mrs Seymer's book, then, is important not only because it is the story of a small body of carefully selected women but also because it deals, in a very engaging fashion, with the antecedents of every nurse who works in our wards today

The Structure and Dynamics of the Psyche

C G JUNG *Collected works* Vol VIII Editors SIR HERBERT READ, MICHAEL FORDHAM, M D, GERHARD ADLER, PH D Translated by R F C HULL London Routledge & Kegan Paul 1960 Pp 596 42s

THIS volume contains eighteen papers setting out Jung's dynamic concepts from the time of his divergence from Freud's psychoanalytical theories to the present time There are seven sections, containing papers grouped together according to theme The opening paper, On Psychic Energy, expounds and clarifies Jung's libido theory, and the final section is occupied by his concept of synchronicity, "an acausal connecting principle" In this long paper, analytical psychology is linked with such apparently unrelated fields as modern physics, astrology, extrasensory perception, and statistics, in a closely reasoned argument

Dew-Line Doctor

GARETH HOWERD London Robert Hale 1960 Pp 191 18s

THE Distant Early Warning Line is a chain of radar stations running, roughly, from the most westerly part of Alaska to the east of Baffin Island Its purpose, like that of the Pinetree and the Mid-Canada lines, which lie south of it, is to give the cities of North America some warning of any aerial attack coming from the direction of the North Pole The construction and maintenance of the line has posed, among other problems, that of the medical care of many small groups of men living hundreds of miles apart under conditions of utter desolation Gareth Howerd was, for a year, one of those who have overcome this difficulty by the use of aircraft and radio, along lines reminiscent of the Australian Flying Doctor service but in a very different climate

His book is for general readers, and his colleagues may regret an absence of clinical detail in the descriptions of the diseases he met But his writing recalls Grenfell's stories of the Labrador, and reads just as fascinatingly

Neurology (5th ed Oxford Blackwell Scientific Publications 1960 Pp 1386 196s)—The latest edition of this well known textbook by *Dr R R Grinker, Prof P C Bucy*, and *Prof A L Sahs* amply maintains the reputation acquired by previous editions Though primarily a work of reference, it is easily read It gives a good account of the relevant anatomy and physiology, a new chapter has been introduced on neurochemistry, and all information is remarkably up to date—a major achievement in so large a book The clinical and pathological descriptions are clear and the illustrations well chosen and well reproduced Though the price is considerable, it represents good value

THE LANCET

LONDON 10 SEPTEMBER 1960

Penicillinase-resistant Penicillin

A NEW penicillin has been prepared which is active against the usual penicillin-sensitive microorganisms and yet resists staphylococcal penicillinase This is a major event in chemotherapy From the information given in the *British Medical Journal* last week and in the three papers appearing in our present issue there is good reason to hope that the new BRL 1241 ('Celbenin', Beecham Research Laboratories) will be a means of controlling the staphylococcal infections which have plagued hospitals throughout the world during the past ten years

The new penicillin is the most important, so far, of the results of the isolation in 1959 of the penicillin "nucleus", 6-aminopenicillanic acid, by BATCHELOR, DOYLE, NAYLOR, and ROLINSON[1] Chemically it is sodium 6-(2,6-dimethoxybenzamido) penicillinate monohydrate In the laboratory it inhibits the growth of coagulase-positive staphylococci in a concentration of about 2–4 µg per ml[2] no matter whether these staphylococci are sensitive to penicillins G and V, the penicillins on which we have hitherto relied, or resistant to these penicillins even in concentrations as great as 1000 µg per ml With cultures of penicillin-resistant staphylococci, the minimum inhibitory concentration of penicillin G is much influenced by the size of the inoculum of test organisms, but with BRL 1241 the inoculum size has very little significance, which is what would be expected, because the BRL 1241 is not destroyed by staphylococcal penicillinase Human serum does not diminish the activity of BRL 1241 In laboratory tests staphylococci developed tolerance to BRL 1241 only very slowly and not to a great extent—certainly not to a point where reduction in its clinical usefulness would be likely Among all the cultures of penicillin-resistant staphylococci that have been tested none has been found with a natural resistance to BRL 1241 There is no cross-resistance between BRL 1241 and chloramphenicol, erythromycin, novobiocin, oleandomycin, streptomycin, or tetracycline Admittedly, penicillinase extracted from cultures of *Bacillus cereus* slowly inactivates BRL 1241, but this does not lessen this antibiotic's efficacy against all staphylococci Though it actually promotes the formation of penicillinase by cultures of staphylococci, BRL 1241 is itself unaffected by the enzyme, even after long incubation in conditions which inactivated a solution of 1 mg of penicillin G in ten minutes Stability of BRL 1241 to staphylococcal penicillinase was unaffected by pH In view of the importance of the bactericidal activity of penicillin, it is reassuring to know that BRL 1241 is bactericidal at concentrations only slightly higher than the minimum inhibitory concentrations

Disadvantages appear to be few Since it is destroyed by the acid in the stomach, the drug is not effective when given by mouth It has to be injected intramuscularly at intervals of 4–6 hours in doses of 1 0 g; and to give the six-day course of treatment advised by the manufacturers will at present cost a hospital £19 10s The large dosage is made necessary by the relatively rapid excretion of the BRL 1241 and by its having only about a hundredth of the activity of penicillin G Its injection seems to cause some pain, but this is of the same order as the pain caused by penicillin G, and there is no evidence of any important difference from other penicillins in its liability to sensitise patients In 2 of 27 children it caused partial replacement of the coccal salivary flora by coliforms, with fatal bronchopneumonia in one of these[3] In the same group 2 superficial candida infections appeared but responded to treatment with 'Nystatin' Nasal staphylococci were not eliminated during parenteral treatment, a point of particular interest in view of the findings of Professor ELEK and Dr FLEMING on p 569

Though chiefly valued for its activity against penicillinase-producing staphylococci, BRL 1241 is active also against many other pyogenic gram-positive cocci including β-hæmolytic streptococci, *Streptococcus viridans*, and the pneumococcus Among the gram-negative microorganisms, BRL 1241 is moderately active against the meningococcus but inactive against the gram-negative bacilli, even against a strain of *Salmonella typhi* which was relatively sensitive to penicillin G[2] Disappointingly, this excludes from its range of activity an important group including not only the salmonellas but also the coliforms, the shigellas, *Pseudomonas pyocyanea*, and *Proteus spp*

The possibilities of the new drug will attract wide attention, and already Professor ELEK and Dr FLEMING have shown how it may be used to eliminate nasal carriers from among hospital staff In this connection, however, we must repeat that no drug or combination of drugs is ever likely to make hospitals safe for patients unless it is used in a far more responsible and intelligent manner than has been usual since antibiotics became generally available Furthermore, aseptic methods will have to be better understood and more faithfully practised Antiseptics will have to be intelligently worked into the gaps which are inevitable in any attempt—however well designed and however scrupulously applied—to make asepsis a method as distinct from an imperfectly understood and often futile ritual Those best acquainted with bacteria are highly impressed by their powers of survival and adaptability, and if we think we can control them simply by an uncritical and extravagant use of drugs we are likely to do no more than write another chapter in the literature of the bacterial ecology of hospitals It is vain to hope that indiscriminate chemotherapy will save doctors, or nurses, or administrators from the need to understand the basis and essentials of bacteriology and to plan their acts accordingly A *rational chemotherapy, on the other hand*—one that depends on a sensible clinical judgment supported by the best help that the laboratory can give—has indeed an essential part to play in controlling hospital infection BRL 1241 offers a hope of controlling the staphylococcus, the organism which has been our chief menace in the postwar years For that we may well be grateful We should see to it that we use BRL 1241 in such a way that we do not simply substitute gram-negative bacilli for gram-positive cocci and allow the plague to rage as before

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[1] Batchelor, F. R., Doyle, F. P., Naylor, J. H. C., Rolinson, G. N. *Nature, Lond* 1959 183 257 see *Lancet* 1959, i 508

[2] Knox, R. *Brit med J* Sept 3, 1960, p 690

[3] Stewart, G. T., Nixon, H. H., Coles, H. M. T. *ibid* p 703

Kidney Homotransplants in Man

SOME of the limitations and potentialities of tissue transplantation are illustrated by two successful attempts at human kidney transplantation In an article on an earlier page of this issue Dr DOSSETOR and his colleagues in Montreal report successful homotransplantation between identical twins The patient, with bilateral chronic pyelonephritis, was grafted with a healthy kidney from her twin sister, and has eventually regained normal kidney function and (after subsequent removal of her own diseased kidneys) normal blood-pressure—both maintained now for more than a year This achievement follows a series of similar operations in Boston by MERRILL and his fellow-workers, who reported their first success in 1956[1] In such operations, involving identical twins, the homotransplant is in effect an autotransplant, and the problem is one of surgical method (here the preliminary animal work of DEMPSTER and his associates[2] is pre-eminent) and of management This approach is gaining acceptance as a possible means of countering severe bilateral kidney disease in the rather rare event of the existence of an identical twin

The identity of twins is probably best determined (as it was in DOSSETOR's case) by exchange of skin grafts Uniovular twins, genetically and therefore antigenically identical, accept each other's living tissues as their own, and a successful exchange of grafts, by proving identity, excludes a major biological hazard of transplantation—the homograft reaction The rejection of skin grafts between *individuals who are not identical twins is a* familiar example of the homograft reaction, which, as we now know from the work of MEDAWAR[3] and his group, is essentially an immunological effect. The host, recognising the donor graft tissue as antigenically different from his own, mobilises a cellular reaction leading to necrosis and rejection of the graft That a second graft from the same donor is rejected at a characteristically accelerated rate suggests that the reaction has an immunological basis, and this has been amply confirmed experimentally It is the more remarkable, therefore, that MERRILL and his co-workers[4] now report a case of chronic glomerulonephritis with uræmia in which they successfully transplanted a kidney from a twin brother whose non-identity was demonstrated by his rejecting a skin graft from the patient An unusually close antigenic relationship was nevertheless indicated by the slowness with which the healthy twin rejected the first skin graft (a second graft was rejected rapidly) and by consanguinity in no less than 25 blood-groups tested The patient himself did not reject his twin's skin graft, but this was not considered evidence of identity, since skin homografts are known to survive exceptionally long in uræmic patients In these somewhat unusual circumstances MERRILL and his colleagues applied whole-body irradiation in low dosage (without marrow infusion) in the hope of averting the immediate anti*body response that would otherwise be engendered by transplanting the healthy kidney This operation* was then successfully carried out and a functioning kidney established A week later, when irradiation had reduced the white-blood-cell count to less than 50 per c mm , the patient's critical condition prompted surgical exploration, which revealed an acute abscess involving the patient's own right kidney This was drained and both his kidneys were removed The spleen only was irradiated after the operation, and within a few weeks the patient's condition improved greatly his white-blood-cell count rose, and his blood-pressure, heart size, and kidney function returned towards normal. Ten weeks after operation he was discharged from hospital, and he has remained symptom-free and active for more than a year Six months after its implantation the skin graft he had received showed slight atrophic changes, suggesting that it was undergoing very slow rejection Biopsy of the transplanted kidney showed cellular changes with the same implication, despite good kidney function This situation was met by repeated low-dose irradiation of the whole body, and by large doses of steroids—a combination which probably prevented a fatal homograft reaction

Experimentally, immunological unresponsiveness to living tissues from another member of the same species can be induced fairly easily in embryonic or newborn animals by introducing living donor cells According to BURNET's[5] concept, developing cells that are immunologically competent may be killed by such continued exposure to antigens against which their specificity is directed, and mature immunologically active cells may be killed by irradiation or by cytotoxic drugs MERRILL and his colleagues suggest that in their case the effects of low-dosage irradiation in reducing the number of mature antibody-forming cells able to respond to the foreign stimulus, and the check to proliferation of immature cells imposed by the implantation of such a plentiful source of antigen as a kidney, together favoured graft survival A similar partial tolerance has been observed by BEILBY et al[6] in a patient in whom agranulocytosis developed during treatment with the cytotoxic drug, chlorambucil A marrow graft from her sister survived, and produced the blood-picture of a red-blood-cell chimæra which persisted for at least nine months, although a skin graft from the same donor was not tolerated The success of implantation depends also on absence of reaction by the graft against the host This—the reverse side of the coin—is well known experimentally with both kidney and marrow, and the apparent absence of such a reaction in these two cases may be associated with a chance distribution of antigens between host and graft favouring survival

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[1] Merrill J P Murray J E, Harrison, J H Guild, W R *J Amer med Ass* 1956 160 277

[2] Dempster W J *Brit J Surg* 1953 40 447 Dempster, W J, Joekes, A M [illegible] *Ann R Coll Surg Engl* 1955, 16, 324

[3] Medawar P B *Proc roy Soc* B 1956, 146, 1

[4] Merrill J P Murray, J E, Harrison J H Friedman E A, Dealy J B, Dammin G J *New Engl J Med* 1960 262, 1251

[5] Burnet M The Clonal Selection Theory of Acquired Immunity London, 1959

[6] Beilby, J O W, Cade I S, Jelliffe A M, Parkin, D M *Brit med J* 1960, i, 96

Supersonic and Hypersonic

AVIATION medicine is entering a new phase This much was made clear by the fifth European Congress of Aviation Medicine, held in London on Aug 29 to Sept 2, and attended by delegates not only from Europe but also from the Commonwealth and the United States The theme of the congress—" the medical problems of supersonic and hypersonic flight " —with its play on Latin and Greek prefixes, introduced a flavour of duality " Supersonic ", as one of the chairmen pointed out, is reserved for speeds up to five times the speed of sound, beyond which " super " gives way to " hyper " Broadly speaking, the adjective " supersonic " invites the noun " aircraft ", " hypersonic " is an unfamiliar word which suggests association with missiles and flight outside the atmosphere There are signs that aviation medicine is about to divide into one branch concerned with the subsonic and supersonic, and a second, almost entirely military, branch concerned with hypersonic flight and hence with space travel

Since the 1914–18 war the air forces have taken the leading part in aviation medicine research, meeting and solving the difficulties of adapting the man to the aircraft and the aircraft to the man years before similar problems arose in civil practice The civil agencies have wisely been content to draw on military knowledge and experience, with minor modifications of equipment and procedure Each major advance in aviation has been well proved in military service before it was adopted for civil use, the sole and tragic exception being the early Comet. This convenient arrangement may now be at an end The airlines and the manufacturers of civil aircraft are turning their attention to the production of supersonic aircraft which, flying at three times the speed of sound (Mach 3), will reach New York $2^1/_2$ hours after leaving London If the normal evolutionary process were to continue, we should expect to see such an aircraft in operation about five years after a supersonic military transport had been proved by the air force, but the first Sputnik and the subsequent remarkable advances in rocket technology have introduced a sharp peak into the curve of progress Though supersonic aircraft have been in military service for some time, they have all been relatively small, carrying a crew of no more than two or three, at the time when large supersonic bombers should have begun to appear in prototype, the rocket made them militarily obsolete and they were abandoned Thus the air force interest passed abruptly from small supersonic aircraft to hypersonic vehicles, and the manifold problems which a large supersonic transport will present are likely to take second place to the fascinating challenge of space flight This may mean that civil aviation will have to stand on its own feet, undertake its own research, and solve its own problems No doubt the civil doctors can count on support from their military colleagues, but this help may be a diversion from the main military effort and on a research basis rather than the sharing of doctrine already established by experiment and validated by practical operating experience Whether the expansion of civil aviation medicine research will come from manufacturers, airlines, or civil additions to the military institutes remains to be seen The American Federal Aviation Agency has formed a Civil Aeromedical Research Institute which, though at present undertaking modest investigations into the methods of selecting air-traffic controllers, may perhaps later turn to the more ambitious problems of the supersonic passenger aircraft

Many of these problems were discussed at the congress There have been differences of opinion, even among those in the counsels of the aircraft manufacturers and the air corporations For example, Mr C S R MARSHALL, of Hawker Siddeley Aviation, feels that a supersonic airliner should have no windows, for the sound technical reason that transparencies do not take kindly to great changes of temperature, and any weakness in the walls of a cabin which will travel at Mach 3 at 70,000 feet is out of the question Mr P G MASEFIELD, president of the Royal Aeronautical Society and a prominent figure in both airline management and aircraft manufacture, says it must have windows, for the sound commercial reason that passengers like to feel they can look out even when there is nothing to see There was no dissent, however, when Mr MASEFIELD, in discussing whether the new airliner should fly at twice or three times the speed of sound, gave as a reason for preferring the latter that no seat in the world really fitted the human posterior for more than two and a half hours

Those who live near airports are already martyrs to the noise which seems inseparable from flying The supersonic airliner is not likely to bring any relief in these areas, but it may make the rest of us a good deal more sympathetic Unless the aircraft stays below the speed of sound until it is near the top of its initial climb, a loud and continuous sonic boom will sweep the countryside over which it flies It is perhaps as well that most of the flight path is likely to be over the sea Inside the cabin, the noise level will be very high unless exceptional measures are taken to insulate the walls

However well an aircraft is designed and built, it is only as safe as the men who fly it Dr E C POULTON reminded the congress that there is a measurable mental load in keeping oneself prepared for something to happen during the performance of a routine task, and this may increase reaction-time by as much as 40% The pilot of a jet aircraft, while attending to the routine conduct of the flight, is continuously alert for the unexpected, which in such aircraft may manifest itself with great suddenness By reacting immediately he can usually prevent an incident from becoming an emergency, or an emergency from becoming a disaster It is, therefore, of the greatest importance to lighten the work load on the crew as much as possible and to make all their equipment thoroughly reliable What applies to the aircrew applies also to the air traffic controllers, whose job is highly responsible and exacting

It is to be hoped that certain subjects not mentioned at the congress are still in the minds of the delegates—especially those who have the ear of the airline presidents There is no reason to suppose that supersonic airliners will be entirely free from accidents, minor if not major Despite the care which will be lavished on automatic control systems, unbreakable cabins, ozone filters, and other elaborate devices, there is still a place for simple life-saving measures The backward-facing seat,[1] properly stressed and anchored to the floor, has saved many lives in subsonic aircraft and will save many more Even supersonic aircraft land at subsonic speeds, and it is just as great a tragedy for a passenger to die an avoidable death at 100 knots as it is to die an unavoidable death at Mach 3

Food and Population

THE principal subject discussed at the meeting of the British Association in Cardiff this week was food-supplies for a world population which is increasing much faster than had been foreseen Since the swelling millions are in part the product of successful preventive medicine, our profession has no small interest in the matter, and it is evidence that our ethos is generally accepted that no speaker even hinted that we should do better if we ceased our attempts to eradicate malaria and such scourges Nobody, in fact, gave more than a passing glance to the possibility that human increase might be checked, as it was for so many centuries, by war or by some fresh plague arising from bacterial or viral mutation

At the moment there is just enough food to serve its purpose Very many people suffer from a shortage of food or a shortage of the right food, but if methods of preservation, transport, and trading were perfected there would be enough for the world population of about 2500 million A reasonable forecast, however, raises this figure to 6000 at the end of the century, and the increase will not be uniform The population of Africa may have multiplied 2 5 times and of Latin America 3 5 times indeed the increase is likely to be most in those continents where the agriculture is least efficient First thoughts suggest that it would be easier to decrease fertility than to increase food production at this rate, but the effects of lowered fertility can be overestimated Were the fertility of the people of India halved there would still be 200 million extra mouths to feed in 1986 Nevertheless the dangers of starvation are so real that search for a method of birth control equally suitable for illiterate peoples is an urgent necessity Some Japanese field trials now in progress could h valuable results

Increasing the world's supply of food is a far m complex problem Seven-tenths of our globe is eit too cold, too dry, or too hilly for farming So countries use almost all their available land some u less than half of it Between different countries the act productivity of what is used may vary by a factor of The potential productivity can usually be judged o where farming has already reached a high standa production in England and Wales could be raised 50 if we wished As Sir ALEXANDER FLECK pointed out, o of the simplest factors limiting yields is the supply nitrogen The Japanese use 100 lb per acre, with much dung as they can collect, on their paddy fiel and obtain 35 cwt of rice The Indians use 1 lb p acre, burn their cow dung for fuel, and obtain about quarter of this yield (One plan for improving Ind. farming is the planting of forests, which will prov wood for fuel to replace the cow dung which wo do more good on the land) Asia uses about 2 milli tons of nitrogen a year 7 million might have an imme ate effect in raising the level of subsistence Nitroge however, cannot be charmed from the air by the wa of a wand To fix 1 ton of nitrogen demands 4 tons coal or 17,000 kilowatts of electricity *India has alrea* begun to develop hydroelectric power on the gra scale and has brown coal in abundance The prospec of atomic power are promising In many places natur gas is allowed to burn to waste

In the West our emphasis is now upon output p man in the East it must be upon greater output p acre In a country where a pair of hands is one of th cheapest commodities, labour-saving machinery ca produce untoward results Tractors have prestige valu as the Russians taught us, but a more efficient ploug to be drawn by bullocks might do more to help th Indian farmer Many of the underdeveloped lands a either too wet or too dry, and water is shifted by metho which seem to have been unchanged since time bega A small, efficient, and foolproof electric pump so cheaply might make great changes Bulldozers may b needed to clear forest and heavy tractors to break har pans, but the designing and making of effective tools fo peasant farmers is one important way in which th West could help

At scientific gatherings it is assumed that all evils wi yield to the magic word "research" equally, that th process will take some time Research on food produ tion is certainly far more urgent than the fashional junketings with space travel, but Prof H D Ka must have startled some of his audience by his dictu that our present knowledge is enough to raise yields b over 50% in most parts of the world It has bee done here and there A fifth of the money now sp by many indigent countries on weapons of war would buy enough improved seed, fertilisers, and barbed w to make a sound start Research there must be, bu the problem is too urgent for waiting

The next step must surely lie with the responsib

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[1] See *Lancet*, 1959, i, 12[illegible]

Governments Not all of them have yet appreciated the consequences of a lower death-rate Some support social structures which make agricultural improvement almost impossible It must be made clear that this is a problem which affects every man, woman, and child alive and all those to be born Those countries which now enjoy easier circumstances can help in many ways There are difficulties in making full use of agricultural surpluses, but it is shameful that in one country malnutrition should be a problem and in another not 200 miles away obesity causes more trouble The richer countries provide advice freely and generously through F A O and W H O They can provide far more more trained staff, more machinery, more money, and more stable markets They must do more than they do in training as agriculturists, engineers, and economists those who are willing to become citizens of the world When they have done their best it is unlikely that it will be enough They must expect no returns and no gratitude, because when the larder is empty we shall all suffer one way or another

Those who founded the British Association would have found this discussion profoundly interesting and probably quite unbelievable MALTHUS had been dead ten years or so, and the advances of science about which they had been hearing made his gloomy forecasts ridiculous We wish they were.

Annotations

RADIOGRAPHY IN COMPRESSED-AIR ILLNESS

A RECENT study [1] of decompression sickness during the construction of the Dartford Tunnel is of special interest because of the radiological investigations, the first to be made during a compressed-air undertaking By their painstaking inquiries, Campbell Golding and his colleagues have provided information which may help to prevent the serious forms of decompression sickness, which are still more common than they should be

A number of Dartford workers had signs of involvement of the central nervous system After one man had been treated successfully in May, 1957, a chest X-ray revealed air cysts in the right lower lobe Although there was at that time no other evidence of an association between decompression sickness and lung disease, the peculiarities of the case pointed strongly to such an association Radiographs of the chest were therefore taken systematically thereafter, and, in February, 1958, a man similarly affected was found also to have a cyst, with a fluid level in it These observations raise the neglected question of the significance of pulmonary changes in decompression sickness Case and Haldane [2] described a pneumothorax developing as a result of exposure to high pressure and subsequent decompression, and they suggested that a cyst or bulla in the lung ruptured A more closely related observation was made by Liebow et al [3] in two men who had air-embolism during training for submarine escape, in which rapid ascents were made in water In one fatal case a broncholith, with air trapped beyond it, was found post mortem, and in the other man a large lung cyst was demonstrated radiologically, which after successful treatment of the air-embolism disappeared

There has been, of course, much work on burst lung, in which the lung parenchyma tears when the intrapulmonary pressure rises But the possibility that a localised air sac may, during decompression, discharge bubbles into the pulmonary veins, without other gross damage, is an important one, for it implies that conditions such as bronchitis or emphysema, in which there might be local air trapping, could lead to air-embolism Disease of the lungs, it has been thought, might hinder exchange of nitrogen between the blood and the alveolar spaces and so aggravate decompression sickness, but the danger of emboli, not from supersaturation of the tissues with dissolved nitrogen but from decompression of trapped air, has not previously been considered and needs to be examined in detail

The Dartford investigators also began a radiographic survey of caisson disease of bone, which is at present best understood in its later (and irretrievably disabling) stages Of 80 men who had had sickness in the form of "bends", but with no permanent after-effects, 10% showed evidence of aseptic necrosis of bones Most lesions in this series were relatively slight, often difficult to detect, and with only a slight resemblance to the advanced disease recorded in the literature Similar minor lesions were also found in 3 out of 20 men who had never had an attack of "bends", although they had had the minor pains which are called "the niggles" and often ignored among compressed-air workers It is known that this necrosis is not accompanied by symptoms unless the articular surface is involved, and the lesions described are presumably at the earliest (and perhaps still reversible) stages of the disease

It is often difficult to take X-rays on the site of a compressed-air working, but the possibility of detecting and excluding men liable to air-embolism of pulmonary origin or to necrosis of bone makes it essential that this work be continued and extended A man who died recently after decompression is reported to have had a lung cyst, and his death may therefore have been preventable When large numbers of men are working in compressed air, it would contribute notably to their welfare (and probably to our knowledge of this condition) to provide an X-ray unit and a full-time doctor on the site, as was done at Dartford

DECIMAL DOSAGE

THE proposed replacement of the apothecaries system by the metric to express the strength of tablets, capsules, and injections in the 1963 edition of the *British Pharmacopœia*,[1] is a major step towards the eventual abandonment of the apothecaries system That this is a desirable aim is now beyond dispute, the General Medical Council, the British Pharmacopœia Commission, and the Pharmaceutical Society are committed to this end, but the mechanics and timing of the final step are highly controversial This week at the British Pharmaceutical Conference in Newcastle upon Tyne, Dr K R Capper [2] pointed out that we are at the half-way stage in the use of the two systems We still expect a dose of scopolamine to be expressed as a fraction of a grain, but we accept pethidine in terms of milligrammes, in an injection containing a mixture of the two drugs the manufacturers tactfully label the ampoules in both systems

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[1] Campbell Golding F Griffiths, P, Hempleman H V Paton, W D M, Walder D N *Brit J industr Med* 1960, 17, 167
[2] Case E M Haldane J B S *J Hyg, Camb* 1941 41 225
[3] Liebow, A A Stark J E, Vogel, J, Schaffer K E *U S Armed Forces Med J* 1959, 10, 265

[1] British Pharmacopœia Commission statement on abandonment of the apothecaries system, September 1960
[2] Capper, K R *Pharm J* (in the press)

In the abandonment of the apothecaries system some of the more complex problems envisaged by Capper concern liquid medicines for internal use a new range of containers would be required, agreement would have to be reached on the capacities of the containers and on the appropriate dose-volumes, legislation would be required to enable a pharmacist to supply the metric equivalent quantity, which might differ by as much as 8% from the amount ordered in the apothecaries system, and the public would need a new range of domestic measures for medicines and to be trained in their use Capper suggests that the apothecaries system should be abandoned in three stages first, tablets, capsules, and injections, secondly, liquid medicines for external use, leaving liquid medicines for internal use as the final stage This he believes could be introduced by September, 1973

How long the apothecaries system survives may depend less on the timing of official pronouncements than on whether aids to its survival are provided—for example, the proposed pharmacopœial table of equivalent quantities, where there is a variation of from 60 to 66 66 mg to the grain to allow particular fractions of a grain to be converted to a metric equivalent in good round numbers The humble gr 5 aspirin tablet will settle the issue in 1963 If the new *B P* requires an aspirin tablet to contain a "metric equivalent quantity" of 300 mg (dose one to three tablets) the apothecaries system will survive, if the truly metric quantity of 250 mg (dose one to four tablets) is required, the end of the apothecaries system will be in sight

PROGNOSIS OF SUBARACHNOID HÆMORRHAGE

A FURTHER study of the prognosis of subarachnoid hæmorrhage has lately been published Pollack and Paddison[1] report a series of 134 cases admitted to the Charity Hospital of New Orleans in the years 1950–56 They applied the recognised diagnostic criteria, excluding all those elderly hypertensives in whom the presence of a primary intracerebral hæmorrhage was presumed, as well as traumatic and neonatal cases The series comprised 82 women and 52 men 57 patients died—an overall mortality of 43% Of the 57 deaths, 38 occurred in the first week after the ictus, and half of these within the first twenty-four hours The outcome of the illness was apparently uninfluenced by sex but was considerably worse if the patient was comatose or semi-comatose and if he was elderly or hypertensive Bleeding recurred in 19 cases, and 13 of these patients died Carotid arteriography was performed in 62 cases, and aneurysms were demonstrated in 33 of these, in another 10 cases aneurysms were demonstrated subsequently at necropsy Hence a total of 44 cases had proven aneurysms, and in this group the mortality-rate was 41%—a figure similar to that for the entire series In 28 of these cases, however, surgical treatment was carried out, a total of 11 patients in the surgical series died, and in these individuals too the outcome was influenced adversely by the presence of hypertension

It is now widely agreed that about 45% of patients with spontaneous subarachnoid hæmorrhage die, many do so within the first twenty-four hours, many more from recurrent bleeding in the first four weeks after the ictus Increasing age, coma, hypertension, and neurological signs indicating intracerebral hæmorrhage or coexisting infarction all influence the outcome adversely[2] [3] With bilateral carotid arteriography many workers have, like Pollack and Paddison, failed to demonstrate aneurysms in much more than half the cases This is partly because vertebral arteriography is not routinely performed, but it may be due also to imperfect radiological technique Perret and Bull[4] have described a series of 210 cases of proved intracranial aneurysm in 89% of which the aneurysm was demonstrated angiographically, they give reasons for supposing that the potential accuracy of the method is about 96% Furthermore the terms "subarachnoid hæmorrhage" and "ruptured intracranial aneurysm" are applied to subarachnoid bleeding due to angiomas and other lesions, and the prognosis and results of treatment can properly be compared only in series in which the cause of the bleeding is known Nevertheless, in the series described by Pollack and Paddison, the accuracy of radiological diagnosis may have been below the ideal, 28 selected cases were subjected to surgical treatment and were yet taken into account when the prognosis of all cases was considered, and the surgically treated cases were subjected to many different operations at different intervals after the hæmorrhage In other words, the findings of this particular study do not help in deciding on the relative merits of conservative and of surgical treatment These remarks are not intended as criticism of the authors' approach, for they reported the facts concerning the recognised methods of investigation and treatment of such cases in their hospital, and there are few hospitals anywhere in the world in which the management of subarachnoid hæmorrhage is any better organised

McKissock et al[5] have published the first results of a carefully controlled trial of treatment In a consecutive series of cases of subarachnoid hæmorrhage, patients in whom surgically accessible aneurysms were demonstrated by arteriography were considered for inclusion in the trial according to a series of strict diagnostic criteria A random selection was then made from cases regarded as suitable for surgical treatment, in such a way that half were subjected to operation and half were treated conservatively Much evidence has recently accumulated to suggest that the difficulties and complications of surgical treatment may depend largely on the situation of the causal aneurysm, for this reason the results for aneurysms in different situations are being analysed separately, and in their initial report McKissock et al describe their results in 94 patients with aneurysms of the internal carotid artery situated at or near the point of origin of the posterior communicating artery 11 patients, who were so ill on admission that they seemed likely to die forthwith, were not benefited by surgical treatment. Of the remaining 83 patients, 42 were treated conservatively and 15 (35%) died In the other 41 cases which were treated surgically (usually by carotid ligation) there were only 4 deaths (10%) These figures clearly indicate that patients with subarachnoid hæmorrhage arising from an aneurysm in this particular situation who survive the first few days can be benefited by surgical treatment The results in patients with aneurysms in other situations are eagerly awaited Meanwhile, studies such as that of Pollack and Paddison remind us that subarachnoid hæmorrhage is a serious condition with a high mortality Clearly a planned routine of investigation and management in specialised centres is indicated

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[1] P[illegible] S L, Paddison R M [illegible] 1960 52, 10[illegible]

[2] Walton J N Subarachnoid Hæmorrhage Edinburgh, 19[illegible]

[3] McKissock, W, Pain[illegible] 1959 [illegible]

[4] Perret L, [illegible] J W D [illegible] 1959 [illegible]

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EXFOLIATIVE CYTOLOGY IN PERNICIOUS ANÆMIA

THE earliest cytological observations in pernicious anæmia (P A.) were, of course, those relating to red blood-cells Besides commenting on changes in mature red cells, Ehrlich[1] applied the term megaloblast to large nucleated precursors present in peripheral blood. Abnormal features were later noticed in cells of the myeloid series Many clinical characteristics of P A, including lingual and gastric atrophy, premature greying of hair, and degeneration of the spinal cord, indicated that this is a general, and not a strictly hæmatological, disease From study of cells exfoliated from various epithelial surfaces, it is becoming clear that cytological abnormalities are widespread and common.

Rubin and Massey[2] observed enlargement of nuclei of gastric mucosal cells obtained by gastric washings in patients with P A. who had already received treatment. Graham and Rheault[3] described enlargement of both nucleus and cytoplasm of squamous epithelial cells that had been shed from mouth or œsophagus in patients with P.A. in relapse. A high prevalence of multiple nuclei was also noted in exfoliated squames from these patients The nuclear abnormalities of squamous cells in P A were confirmed by Rubin[4 5] and Massey and Klayman,[6] who suggested that these occurred in other megaloblastic anæmias In gastric washings on patients with P A some of the gastric epithelial cells were found to be abnormal, having either a "bland" nucleus or an "active" appearance, with clumping of chromatin and prominent nucleoli Rubin[4] remarked, however, that "active" cells may be found in washings from patients with simple achlorhydria without P A. Such cells do not necessarily disappear with treatment, and Henning and Witte[7] and Schade[8] emphasise that they are not pathognomonic of P.A.

Boddington and Spriggs[9] studied cells from nasal mucosa, urinary tract, and vaginal and gastric epithelial surfaces They concluded that widespread epithelial-cell changes might take place in P.A. and that these were reversed by treatment, but that the appearances were too inconstant and non-specific to have much diagnostic value. Squamous cells from buccal mucous membrane are the most easy to examine, and, by measuring nuclei, Boen[10] and Farrant[11 12] have confirmed that abnormalities of shape and size occur in P.A. Boen et al[13] described a patient with neurological changes of subacute combined degeneration of the cord, in whom the hæmoglobin level and marrow were normal The serum-vitamin-B_{12} level was reduced, and the buccal epithelium showed nuclear pleomorphism and giant nuclei, which reverted to normal after a week's treatment with vitamin B_{12} Boddington and Spriggs[9] refer to a case in which the epithelial changes strongly suggested deficiency of vitamin B_{12}, an initial marrow examination was not diagnostic, but the diagnosis of P A was confirmed by a second marrow aspiration.

Clearly the cytological examination of buccal epithelium is only occasionally of diagnostic value in cases of suspected vitamin-B_{12} deficiency But it does seem that vitamin B_{12} may be necessary for the normal maturation of many cells besides red and white cells, and that it may be an essential factor for normal nuclear metabolism. Mallarmé[14] viewed P A. as a nutritional cytological dystrophy, and the latest evidence supports this view

TOXOCARAL PSEUDOGLIOMA OF THE RETINA

THE differential diagnosis of glioma of the retina presents two problems it must be distinguished, first, from non-malignant conditions, and secondly from the different types of pseudogliomatous reactions which themselves are not easily recognised. Both these difficulties are well shown by a study of 53 cases in children up to 5 years of age in whom an eye was enucleated on the suspicion of retinoblastoma[15] The diagnosis was found correct on histological examination in 24 cases, but in the remaining 29 cases a mass of inflammatory reactions and congenital anomalies—some fairly well defined, others ill understood—were found In this series, from two Central European centres—Rostock and Magdeburg—no retrolental fibroplasia was observed

In 1950 Helen Wilder[16] drew attention to the presence of nematode larvæ in a series of pseudogliomas studied histologically The unexpectedly high rate of such findings raised the question whether her material was representative, but Wilder herself held that nematodes were an important cause of blindness in American children Six years later Nichols[17] re-examined five of the cases in Wilder's series and identified the nematode as the second-stage larvæ of *Toxocara canis* This established for the first time that the dogworm could infect the human eye Confirmation came, in 1959, from Irvine and Irvine,[18] who observed *T canis* in an eye which had been diagnosed clinically as the seat of retinoblastoma. Further support now comes from a study of four cases by Ashton[19] These were obtained from the material at the Institute of Ophthalmology in London and concerned children who had had an eye excised on the suspicion of tumour The children hailed from London, Bristol, Taunton, and Kilmarnock, and were aged 8, 16, 11, and 4 years respectively The diagnosis in each case had been difficult and uncertain both clinically and histologically Re-examination of these eyes now reveals that they are affected by solitary retinal masses caused by toxocara, histologically demonstrable

Toxocara is as widely prevalent in dogs in this country as elsewhere, and the recognition that ocular toxocara infection does occur in this country raises the question of the frequency and manifestations of this infection here as a general disorder as well as an ocular disturbance. Diagnosis is still difficult, and for the present the one laboratory finding that may reinforce the tentative diagnosis of ocular toxocara infection is a high eosinophil-count.

SIR WILFRID LE GROS CLARK has been elected president of the British Association for the Advancement of Science for 1961

THE death is reported from Metz of Dr MARJORY WARREN, physician to the geriatric unit of the West Middlesex Hospital, from injuries received in a road accident

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Special Articles

METAMORPHOSIS OF A MENTAL HOSPITAL

Application of McKeown's Comprehensive Unit

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LANCASTER MOOR HOSPITAL, LANCASTER

THE idea of a comprehensive hospital is not new It has been considered and mooted for some time In 1958 it was cogently described by McKeown, who classified patients into four groups

Group 1 those who need full hospital facilities, such as frequent medical attention and skilled nursing

Group 2 those who need limited facilities, such as simple nursing, washing, dressing, feeding, bowel and bladder attention but no mental supervision

Group 3 as in group 2 but with mental supervision

Group 4 those who need no special medical or surgical facilities and who remain in hospital chiefly for social reasons

McKeown's proposals were published at about the same time as we were considering the future policy and planning of this mental hospital of over 2000 beds Because of the shift of emphasis to outpatient treatment, the more potent treatment of inpatients, and a more-than-averaged-aged patient population our numbers between 1954 and 1959 fell from 2784 to 2143 with the almost unheard-of possibility of wards becoming empty Early in 1959 the speed of this change was slowed by the addition of another quarter of a million to our catchment population, which doubled overnight our potential patient intake This slowed but by no means stopped the run-down, because its effects were partly offset by the policy of our regional hospital board of opening psychiatric units attached to general hospitals Such units, when properly staffed and vigorously used, can reduce admissions to mental hospitals to a very small number

We thus found ourselves with large buildings, most of which had received a great deal of structural renewal and maintenance, together with elaborate and efficient services of heating, electricity, water, and so on We had first-class pathological, physiotherapy, surgical (particularly neurosurgical), and neuroradiological facilities and equipment Even more important were our human resources in the form of the nursing staff, many of whom, especially on the male side, were doubly trained And a definitely falling patient population

Had we any doubts about the trend these were removed when we considered the implications of the Mental Health Act Here was a deliberate and planned intention of a change of emphasis from hospital to community care with funds potentially available to set up hostels for people who could quite well live outside the hospital if accommodation were available

Faced with these facts we tried to draw up a definite and coherent policy and plan which would make good use of our accommodation, nursing staff, and ancillary services, and at the same time cater for a definite need in the community This is the nexus of the whole plan We are catering for needs that have been apparent and known for some time We are not trying to revive a corpse or shore up, for specious reasons, buildings that ought to come down Nor indeed are we attempting to make the hospital " play Hamlet after the age of 60 " against the advice of Beerbohm Tree We believe that, though its function is changing, the major part of the hospital itself will continue to supply a service which will be necessary so long as there are people who need hospital care and attention

METHOD OF REORGANISATION

An isolated building with about 200 beds hitherto occupied by women patients (many of whom could have been discharged had there been anywhere for them to go) was transformed with little effort into a psychiatric admission unit for about 110 women and 90 men To this unit all our admissions go at present, except for a few aged men who are admitted to their own detached ward of undesignated beds (90) and a small number of aged women who also have their own undesignated geriatric ward (66)

Our psychiatric admission unit, therefore, caters for the inpatient treatment of patients coming from a population of half a million people This is less than $^1/_2$ bed per 1000 of the population instead of 3 beds per 1000 population usually asked for in Western Europe Yet so far our unit has not been overcrowded Our experience is that it can cope with the catchment population provided that there is a reasonable geriatric service which prevents small numbers of psychiatric beds being blocked by aged people

The geriatric service we have provided ourselves by reclassifying wards and patients We now have 300 beds for male geriatric patients and 500 for females, including the two undesignated units already mentioned If a geriatrician should be appointed for the area, a ready made series of wards or centre will be available for him

A more detailed survey of one of our male geriatric units *might be of interest*

This is our 90-bedded detached building called Cas House An analysis of its bed occupancy shows the following McKeown groupings

McKeown group	No of patients	Types of illness
1	19	Post-thrombotic arteriosclerosis of different kinds mostly needing bed treatment
2	36	Senile arteriosclerotic showing variety of [illegible] e g, parkinsonism, Paget's disease
3	8	As above plus chronic schizophrenics whose acute illness has disappeared All are institutionalised
4	27	Many have very slight memory impairment Mostly in unit for social reasons

The unit has its own 2 occupational therapists and is run by 2 charge nurses with 2 deputies and a nursing service from the hospital on demand *The doctor in charge* is a local general practitioner on a twenty-four-hour call with his partners It has none of the gentle-decay type of atmosphere of many purely hostel units, and many of the group-3 and group-4 patients are keen to help those of their brethren who are more incapacitated than themselves For the past year the unit has never had a bed empty for longer than twenty-four hours

For so-called chronic and long-stay mental patients we still keep about 130 male and 400 female beds When reclassifying our patients we estimated that about 15 of the men and 20% of the women were in fact defectives who had been transferred from the Merseyside conurbation during war evacuation from hospitals in that area and whose relatives are now apparently non-existent

Another pressing need has been beds for chronic physically sick patients By reclassification and in[illegible] transfers, a large detached building of about 80 beds was cleared for this purpose. It was necessary to install two or three sluices, toilets, and so on, but this was a minor task. So far, 30 chronic physically ill men have been nursed there, most of whom have needed full hospital nursing and medical facilities It is considered that this unit meets the chronic medical needs of the male population of this area. Occupational therapy is given for as many of these patients as are able to carry it out.

In the Manchester region there was a waiting-list of over 1000 patients for mental-deficiency beds We have accepted 50 defectives who need complete nursing facilities—so-called "cot-and-chair" defectives who fell into group 1 Three of our male nurses were seconded to a mental-deficiency hospital for a year's training and they are now working under the clinical supervision of a consultant from that hospital

We hope to set up a blood-transfusion unit in another part of the hospital Technical requirements have delayed its opening, but it will come into operation some time this year, using a building of sound construction but empty of patients

Other buildings house tuberculous and gastrointestinal patients These at present are, or have been, mentally ill, but in these two wards (male and female) separate accommodation supplies clinical and pathological services which could in the future easily and efficiently be used for fresh non-mental cases

We have tried to make the scheme comprehensive but flexible, and if the number of mentally ill patients in need of hospital accommodation continues to fall, the vacant places might well be used for other real, and sometimes pressing, needs—e g , postoperative orthopædic patients

MEDICAL SUPERVISION

Most mental hospitals, especially in the North, are short of doctors About eighteen months ago it was calculated that each doctor in this hospital, assuming he worked his full sessions, without any holidays or extramural activities such as outpatients, was able to give a patient about 4 hours per annum In practice, of course, many patients did not receive as much attention, which from any point of view was indefensible

By reclassifying our patients, and particularly by remembering that old people were old people with a variety of organic disorders and not merely "psychogeriatric", we were able to introduce this large group to general practitioners who were interested in geriatrics

Three junior psychiatric posts—almost never filled or filled in a very desultory way—were broken up into clinical-assistant sessions for general practitioners There are now six of these G P s, and each has about 200 geriatric patients under his general supervision for the whole twenty-four hours He is responsible for their clinical, investigational, and therapeutic care, and has the whole range of the hospital's consultant services at his disposal (The medical superintendent still has statutory obligations towards many of these old people who have been, at some time or another, considered to be mainly psychiatric problems)

The introduction of general practitioners has been an unqualified success To their task of looking after the chronic physically ill, including tuberculosis and gastro-intestinal patients and the old people, they bring a practical knowledge and stability rarely found among juniors in large mental hospitals This move has been one of the best sequels to our reorganisation and it has awakened an entirely new therapeutic hopefulness among the nurses and the patients

The psychiatric staff (consultants, S H M O s, and two registrars) freed for the first time from non-psychiatric duties, are able to spend all their time in the outpatient departments, the admission hospital, and/or the long-stay annexes in which most of the difficulties and problems are psychiatric

Though no-one can be antagonistic towards the concept of the "therapeutic community" or to Bickford's (1955) views on the treatment and nursing of the chronic mentally sick, nevertheless we believe that it is important to avoid adding to the numbers of the long-stay mental patients We believe simply that this addition is unnecessary if we apply modern treatment methods properly and vigorously, with the help of good outpatient facilities, day hospitals, community care, and the provisions of the Mental Health Act of 1959 Furthermore, as we have tried to show, the most obtrusive problem in this hospital is the institutionalised geriatric patient with little or no evidence of psychiatric illness He belongs properly to organic or structural medicine.

By returning psychiatrists to the practice of psychiatry, we have not only benefited ourselves (and the psychiatrically ill, especially the neurotic who now feels that his doctor has at last some time to give to him), but we have extended McKeown's concept, so that it might now read *not only should there be one type of hospital, but all doctors should work there whether full-time as consultants or part-time as family doctors*

Such an arrangement could remove many of the anomalies and difficulties of finding junior staff and produce a vast, almost untapped, reservoir of ability much greater than most hospitals have had for years It is in fact a proposal for a partial return to "pre-1948" when many family doctors worked in hospitals

Our thanks are due to the regional hospital board and the hospital management committee for their wholehearted support We also wish to thank Mr H Carr, F H.A , hospital secretary, and Mr W Lewty, B SC , the hospital engineer

The introduction of the scheme has meant an almost cataclysmic upset amongst the patients and nurses Both have cooperated enthusiastically, and indeed at times insisted on overrunning the programme of events Without these two groups the scheme would have completely failed

Last, but not least, our thanks are due to our own colleagues who helped to put the plan into operation effectively and efficiently

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" Science is not an autonomous realm of knowledge, governed by immutable rules, but is a way of doing intellectual business If I may be allowed an analogy, it is like the Stock Exchange The price of a particular share on a particular day is not fixed by any one individual, although it may be greatly influenced by big buyers and sellers The truth value of a scientific theory, also, is not predetermined by the genius of its discoverer but depends on the price which other scientists will put upon it. In science, as on the Stock Exchange, one is bound to be absolutely fair and honest because the long-term profits of decent trading are greater than the immediate gains of fraud. But honesty will not protect any of us, individually, from errors of judgment, in the long run, the market price is the only fair price There may perhaps be better social means than the Stock Exchange for maintaining the economic health of the nation, I doubt if there is any better instrument for achieving reliable knowledge of the world than a freely co-operating community of scientists —JOHN ZIMAN *Listener*, Aug 18, 1960, p 252

Before Our Time

WRITER, DOCTOR, AND PATIENT

Anton Chekhov was born a hundred years ago into a literary epoch that was dominated by tuberculosis. To his generation of writers tuberculosis was an attitude of mind and a way of living, a stimulant of deep emotions, passions, and inspiration, and it was Providence's favourite disguise, both in fiction and in reality. Shortly before he died Chekhov wrote that he had taken Medicine as his wife and Literature as his mistress, and it might have been a singularly happy *menage a trois*. But at the age of 23, as a starving and high-minded medical student in Moscow, he was already spitting blood "regularly in the wet season" and he was plagued by recurrent laryngitis.

By then he had written scores of short stories—some of them real medical-student literature, brimming with anatomical detail. Dr Toporkov, one of his creations in *Late Flowers*, percusses and auscultates at length, he notes dullness on the right and crepitations on the left, and bronchial breathing spreading to both bases. But medical peepshows of this kind are unprophetic of Chekhov's writings as a qualified doctor. To his non-medical contemporaries the contrast between the stark facts of the case-sheet and the complexity of life was irresistible. Turgenev rarely missed a chance to spice his tales with clinical irrelevances, and Tolstoi relished medical jargon. Dr Chekhov's characters, on the other hand, are merely ill: they suffer pain, weakness, and fever, they lie awake at night and cough torments them by day, and they die hoping.

> The poor schoolmaster Sisoiev, for example, feels a trifle weary, but on no account would he miss the banquet that is to be given in his honour. Putting on his spotlessly polished black boots exhausts him so much that he has to rest for a while, and in front of the director's apartment he is seized by a bad bout of coughing. So bad that he flings his stick to the floor and his cap drops off his head. When his host and fellow teachers and the school-inspector himself hurry out of the flat he sits gasping at the top of the stairs, covered in sweat. An unfortunate and undignified contretemps, he meditates, when eventually he gets home. He gazes at his drawn, shadowed face in the mirror. "But I'm making a fuss. In fact, my colour is better than it's been for months. If only the gastric catarrh wouldn't bring on that wretched cough." He decides to spend the summer in the South. If only he could scrape up the necessary money.

It might be an episode from one of the middle-aged Chekhov's letters.

* * *

After qualifying he settled in Szumi near Kharkov, renowned for its health-giving climate. But he could not stick his isolation from the country's literary hubbub for long. He returned to Moscow, wrote several short plays, and became a prolific contributor to newspapers and magazines. His favourite brother died in 1889 from tuberculosis, but within a year, with the calculated recklessness of the tuberculous, he set out on a tour of Far Eastern convict colonies. Even by the heroic standards of 19th-century journalism, this was a nightmare journey. He finished *[illegible]*—for an age of social ferment a strangely uncommitted piece of reporting—but on his return he was coughing up blood every morning and became so weak that he could no longer leave his room. This was the classical picture of the young, consumptive, soulsick writer, suddenly brought face to face with the realisation that his years (or months, or weeks, or days) were numbered. In Moscow's bleak midwinter Chekhov was easily persuaded to seek a new lease of life in Italy. A hectic three-months tour of Lombardy, Florence, Rome, and Naples became his honeymoon with death.

He is the hero of *The Tale of the Unknown Man* who develops pneumonia in Venice. It is an odd, nocturnal illness. The Unknown sits at his desk, resting his head in his arms; a dry, lancinating cough keeps him awake until his feet feel like lead, and his neck and back ache, and perspiration runs down his burning forehead. But the daylight is too precious to waste: the backwater canals and piazzas bubble with excitement and adventure. To outsiders such life appeared effervescent, and death at the end seemed tragic and inconsequent. But outsiders could not be trusted: their judgment had been warped by their regulation ten hours' sleep and their perception blurred by crude physical health. The sick man looked at them with ironic detachment: his own extravagances may have been pointless but they were not futile—neither farce nor grand tragedy but a gentle *commedia lacrymosa*.

After a riotous honeymoon even Chekhov's relation with death mellowed into a middle-aged love-affair. Three years later, now a Government dispensary doctor in Melihovo in the Southern Ukraine, he writes: "I'm pretty fit on the whole. True, I cough rather more than I used to and I get short of breath easily, but my consumption is not galloping away with me yet." And a year later: "I'm much better since I cut down my smoking to a cigar a day. What do I do? Well, I do my rounds and tend myself in between and, of course, we're all waiting for the cholera." This is the period of his great autumnal plays, which he peoples with men and women who are doomed like himself, but who must not be taken tragically. "We shall go on living," says the plain Sophia when she is left alone with Uncle Vanya, "and when the time comes, we shall die submissively." And amid all the slow decay and quiet nostalgia for the passing of beauty, there is always hope—the promise of spring, a certainty that happiness is just round the corner. To the go-getting world beyond the footlights such happiness ought to seem unreasonable, even ridiculous, but it never does. We sense that these people, as they drift from nowhere to nowhere through unchanging lives, have somewhere, somehow, discovered the secret of real change. The key to that secret is missing from our world, and they may have mislaid it themselves, but from their world it is not altogether lost.

* * *

During the years of remission, tuberculosis vanishes from Chekhov's writings: then suddenly, in 1891, it kills Kovrin, the hero of the *Black Monk*. A few months later, walking through the Ermitage, Chekhov, too, has a hæmorrhage and collapses in front of Titian's *[illegible]*. He rallies, but he reaches Moscow too weak to get off the train. And so the physicians at the Ostrumov Clinic take over from the doctor-writer.

> Drawn face. Wasted body. Weight 33 kg., height 186 cm. Extreme pallor, irregular, thready pulse. Poor chest movements with signs of cavitation at both apices. Sputum teeming with Koch's bacilli.

"My crotchety lungs played me up just when I needed them badly," is the patient's comment a week later, "and my learned friends are pouring gallons of *kumiss* into me and insist that I must change my way of life." Despite the mockery, he was a good patient, and from his letters it is hard to say what he thought of his professional colleagues. On the stage they are a mixed bunch. Lvov is a prig—estimable but harsh, intolerant, and an inverted snob. Dorn is a faded provincial *jeune premier* [illegible]

On reading these statements one wonders whether even e clear minds of the leader writers of the *Times* and the *Economist* become clouded by emotion when contemplating the prospect of actually paying for the Health Service. If this is so, it is hardly surprising that the doctors themselves are confused when considering problems intimately related to medical economics.

Richmond J. R. SEALE

MORE CHROMOSOME ABNORMALITIES

SIR,—May I comment on your leading article of July 23.

Sex chromatin is visible because it is positively heteropyknotic, which means that it is condensed and therefore stains intensely when the rest of the chromatin is relatively diffuse. But the phenomenon of heteropyknosis was actually discovered in the male. It was found at the beginning of the century that the X chromosome in the spermatocytes of insects "becomes greatly condensed and often rounded in form, stains intensely with basic dyes and thus appears as a karyosome or chromosome-nucleolus which shows the sharpest contrast to the thread-like or diffuse, and lightly staining ordinary chromosomes (autosomes)."[1] The two X chromosomes of the female do not show heteropyknosis. The same applies to mammals.[2] According to Schrader[3] "Perhaps the most striking characteristic in the behaviour of the sex chromosomes is their heteropyknosis in the heterogametic sex, especially during the meiotic stages." He brings a considerable amount of evidence that heteropyknosis occurs when a chromosome has no homologous partner.

Recently interest has shifted to the sex chromatin of the female. It would seem as if the situation here is precisely opposite, since heteropyknosis occurs only if at least two X chromosomes are present. If a working hypothesis to cover the known facts is required at present, I suggest that it might be sought along the following lines. Heteropyknosis in the male occurs during meiosis, when the autosomes are paired and only the X chromosome is single. The sex chromatin of the female is seen only in non-dividing cells, where the presence of two X chromosomes results in heteropyknosis, possibly because the autosomes are unpaired. If one were to assume a slight difference in the timing of the two X chromosomes, one of them would become heteropyknotic in the presence of the homologous partner, but having done so, the second X chromosome has no homologue and therefore does not condense. This would explain Ohno's[4] demonstration that in female rats only one of the X chromosomes is heteropyknotic, as well as the fact that in diploid cells there seems to be one chromatin body less than the number of X chromosomes present.

Schrader[3] wrote in 1928: "All in all then we know astonishingly little about the cause of heteropyknosis. . . . Its answer no doubt involves a much more thorough knowledge of the structure and physiology of chromosomes than we now possess." In 1960 this is still true. But we know now that in different circumstances heteropyknosis may occur in cells containing a single X chromosome or in cells containing two X chromosomes, and this should be taken into account when formulating a hypothesis regarding the nature of sex chromatin.

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SHORTAGE OF RADIOGRAPHERS

SIR,—May I concur entirely with the remarks and suggestions put forward by Mr. Hutchinson (Aug. 20), and also propose that the same measures and views equally apply to the shortage of physiotherapists.

Sudbury,
Suffolk. DAVID WHITE

OPERATING ON THE WRONG LIMB OR DIGIT

SIR,—The council of the Medical Defence Union is becoming increasingly perturbed by the number of occasions on which it is confronted with a patient's claim for compensation based upon the fact that an operation was performed on the wrong limb or digit. During the past twelve months the Union has dealt with no fewer than nine such claims and it is hardly necessary to say that cases of this sort are quite indefensible.

Such mistakes are not infrequently due to an error in the clinical notes—e.g., the word "right" instead of "left" is entered or, in the case of a finger or toe, the digit is wrongly numbered or described in the notes. The mistake is sometimes due to the fact that the wrong limb or digit is prepared for operation. In so far as the designation of fingers is concerned, the council reiterates[1] its suggestion that, in order to avoid any possible misunderstanding, the affected digit should be described as the "thumb", the "index finger", the "middle finger", the "ring finger", and the "little finger" and not as the "first", "second", "third", &c., finger.

In view of its recent experience the council of the Medical Defence Union considers it is only proper that the attention of the profession should be drawn to these unfortunate and avoidable mishaps.

PHILIP H. ADDISON
London, W.C.1 Secretary, Medical Defence Union.

TREATMENT OF PAIN IN PREAXIAL BORDER OF UPPER LIMB

SIR,—For a variety of reasons the article of Aug. 13 by Miss Wareham and Mr. Farrow was disappointing. This is a subject on which one would like to know more.

To begin with, it would have been interesting to know for how long and how frequently the traction was applied. Can the general practitioner use this method of treatment?

In most of such cases both the acromioclavicular and radiohumeral joints are involved to some extent, but they are not mentioned. They ascribe limitation of shoulder movement "to an associated adhesive capsulitis." Is this secondary to the cervical spondylitis, a neurotrophic phenomenon, or what? Capsulitis would suggest that there is an acute inflammation of the capsule amounting to an acute arthritis. If this were so the least movement would be excruciating. Anyway, such inflammations are unlikely to be secondary to lesions of the cervical spine. It is more likely that there is reflex motor irritation of the constituents of the musculotendinous cuff of the shoulder, but to describe this as adhesive capsulitis would be absurd.

Manipulation was mentioned, but not what sort, nor what objective results it achieved.

The possibility of symptoms arising from angulation of the nerve "around the neurocentral joint, and an excrescence from here . . ." is scarcely valid. If X-rays are repeated as soon as the patient is symptom-free, the appearances will be found to be unchanged. Osteophytic new growth or the osteochondrotic or sclerotic proliferation round chronically arthritic joints merely appears where there is room for it. (The use of the word neurocentral as applied to Luschka's joints implies that it is a defect of union between centres of ossification, whereas it is a joint between the uncinate process of one vertebral body with the body above. I thought they were called the unco-vertebral joints.)

Probably what their treatment has achieved is the relief of a group of restrictive joint lesions affecting the intervertebral joints of the fifth, sixth, and seventh cervical vertebræ. But one cannot be sure even of that, because the 14 lb. traction would be palpably effective down to the third or fourth cervical vertebra. For example, it is quite possible that the traction whether the factor responsible is the richness of the food or the emotional impact of the *addition* If you smoke too much or if you refrain too strictly from smoking, if you are too busy or too idle, if, in fact, you do anything to disturb the anxious homœostasis of the bowel, however indirectly, retribution will descend It is a gastrointestinal purgatory, all that may be done is to regulate one's life in such a way that one may eventually pass through it to a higher state of being

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[2] Guenin, H. A. *J. Genet.* 1948, 49, 23.
[3] Schrader, F. Die Geschlechtschromosomen. Berlin, 1928.
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The old countryman, complaining of his indigestion, said "I'm bringing up so much gas, doctor, I think it must be gasteritis "

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Letters to the Editor

TOO FEW DOCTORS

SIR,—In their article of Sept 3 on the supply of doct in Britain, Professor Lafitte and Professor Squire indic that " unless there is immediate action, something l a crisis in the supply of doctors may emerge arou 1965 " Their reasoning appears to be irrefutable, and there is little prospect of any immediate action, t prediction will doubtless be confirmed in due course

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We now know that the excessive economic burden of the N H S is, and always has been, a myth Indeed, in the years when the Guillebaud and Willink Committees were set up, the Health Service was absorbing a smaller share of the nation's resources than medical care had absorbed in Britain in the 1930s when financed by charity, local authorities, and patient payments The Willink Committee did not know this at the time, and as it was largely composed of doctors, was hardly in a position to analyse the relevant economic data Their information about the wider economic aspects of the N H S would have been drawn from sources such as the *Times* and the *Economist* What do these sources tell us of the economics of medical care ?

The *Times*, on March 29, 1958, criticised the health service estimates for 1958–59 as excessive because the gross cost would rise by 40% from 1953–54 to 1958–69, while the retail price index was rising by only 20% Although admitting that " health service costs have no close connexion with the trend of retail prices ", it considered that " the rising health bill has plainly gone beyond what price changes would justify " This is curious reasoning, because medical care in the N H S is not for sale, and therefore the concept of price is irrelevant—one must look at incomes, not prices In addition, the year taken for comparison (1953–54) was the year when the proportion of national income absorbed by the N H S was at its lowest—the trough which preceded the inevitable rise, as described recently [1]

The *Economist*, on July 5, 1958, poured scorn on the suggestion " that the burden on the country's economy (had been) made no greater by the substitution of a publicly provided service for one that was privately paid for " In search of economies it went on to wonder " whether money could not have been wrung out of (the hospital service) by a more realistic squeezing of hospital budgets " The opinion of the *Economist* that a tax-financed health service costs more than privately financed medical care is a good example of the opinions which can be held when one does not bother to verify them by observation

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[1] Seale, J R *Lancet*, 1960, i, 1349

On reading these statements one wonders whether even e clear minds of the leader writers of the *Times* and the *conomist* become clouded by emotion when contem- ating the prospect of actually paying for the Health ervice If this is so, it is hardly surprising that the ctors themselves are confused when considering roblems intimately related to medical economics

Richmond. J R SEALE

MORE CHROMOSOME ABNORMALITIES

SIR,—May I comment on your leading article of ly 23

Sex chromatin is visible because it is positively hetero- yknotic, which means that it is condensed and therefore stains tensely when the rest of the chromatin is relatively diffuse. ut the phenomenon of heteropyknosis was actually discovered the male. It was found at the beginning of the century that e X chromosome in the spermatocytes of insects "becomes eatly condensed and often rounded in form, stains intensely ith basic dyes and thus appears as a karyosome or chromo- me-nucleolus which shows the sharpest contrast to the thread- ke or diffuse, and lightly staining ordinary chromosomes utosomes)"[1] The two X chromosomes of the female do not how heteropyknosis The same applies to mammals[2] Accord- g to Schrader[3] "Perhaps the most striking characteristic in e behaviour of the sex chromosomes is their heteropyknosis the heterogametic sex, especially during the meiotic stages" e brings a considerable amount of evidence that hetero- yknosis occurs when a chromosome has no homologous artner

Recently interest has shifted to the sex chromatin of the emale It would seem as if the situation here is precisely pposite, since heteropyknosis occurs only if at least two chromosomes are present. If a working hypothesis to cover he known facts is required at present, I suggest that it might e sought along the following lines Heteropyknosis in the ale occurs during meiosis, when the autosomes are paired nd only the X chromosome is single. The sex chromatin of he female is seen only in non-dividing cells, where the resence of two X chromosomes results in heteropyknosis, ossibly because the autosomes are unpaired If one were to ssume a slight difference in the timing of the two X chromo- omes, one of them would become heteropyknotic in the presence of the homologous partner, but having done so, the econd X chromosome has no homologue and therefore does ot condense This would explain Ohno's[4] demonstration hat in female rats only one of the X chromosomes is hetero- pyknotic, as well as the fact that in diploid cells there seems to be one chromatin body less than the number of X chromo- somes present

Schrader[3] wrote in 1928 "All in all then we know astonishingly little about the cause of heteropyknosis   Its answer no doubt involves a much more thorough knowledge of the structure and physiology of chromosomes than we now possess" In 1960 this is still true. But we know now that in different circumstances heteropyknosis may occur in cells containing a single X chromosome or in cells containing two X chromosomes, and this should be taken into account when formulating a hypothesis regarding the nature of sex chromatin

Galton Laboratory,
University College,
London, W C.1

URSULA MITTWOCH

SHORTAGE OF RADIOGRAPHERS

SIR,—May I concur entirely with the remarks and suggestions put forward by Mr Hutchinson (Aug 20), and also propose that the same measures and views equally apply to the shortage of physiotherapists

Sudbury,
Suffolk.

DAVID WHITE

---

[1] Wilson, E. B The Cell in Development and Heredity New York, 1925
[2] Gluenin, H. A. *J Genet* 1948, 49, 23
[3] Schrader, F Die Geschlechtschromosomen. Berlin, 1928
[4] Ohno, S, Kaplan, W D, Kinosito, R. *Exp cell Res* 1959, 18, 415

OPERATING ON THE WRONG LIMB OR DIGIT

SIR,—The council of the Medical Defence Union is becoming increasingly perturbed by the number of occasions on which it is confronted with a patient's claim for compensation based upon the fact that an operation was performed on the wrong limb or digit During the past twelve months the Union has dealt with no fewer than nine such claims and it is hardly necessary to say that cases of this sort are quite indefensible

Such mistakes are not infrequently due to an error in the clinical notes—e g, the word "right" instead of "left" is entered or, in the case of a finger or toe, the digit is wrongly numbered or described in the notes The mistake is sometimes due to the fact that the wrong limb or digit is prepared for operation In so far as the designation of fingers is concerned, the council reiterates[1] its suggestion that, in order to avoid any possible misunderstanding, the affected digit should be described as the "thumb", the "index finger", the "middle finger", the "ring finger", and the "little finger" and not as the "first", "second", "third", &c, finger

In view of its recent experience the council of the Medical Defence Union considers it is only proper that the attention of the profession should be drawn to these unfortunate and avoidable mishaps

London, W C.1

PHILIP H ADDISON
Secretary, Medical Defence Union.

TREATMENT OF PAIN IN PREAXIAL BORDER OF UPPER LIMB

SIR,—For a variety of reasons the article of Aug 13 by Miss Wareham and Mr Farrow was disappointing This is a subject on which one would like to know more

To begin with, it would have been interesting to know for how long and how frequently the traction was applied. Can the general practitioner use this method of treatment?

In most of such cases both the acromioclavicular and radiohumeral joints are involved to some extent, but they are not mentioned. They ascribe limitation of shoulder movement "to an associated adhesive capsulitis" Is this secondary to the cervical spondylitis, a neurotrophic phenomenon, or what? Capsulitis would suggest that there is an acute inflammation of the capsule amounting to an acute arthritis If this were so the least movement would be excruciating Anyway, such inflammations are unlikely to be secondary to lesions of the cervical spine It is more likely that there is reflex motor irritation of the constituents of the musculotendinous cuff of the shoulder, but to describe this as adhesive capsulitis would be absurd

Manipulation was mentioned, but not what sort, nor what objective results it achieved

The possibility of symptoms arising from angulation of the nerve "around the neurocentral joint, and an excrescence from here   " is scarcely valid. If X-rays are repeated as soon as the patient is symptom-free, the appearances will be found to be unchanged. Osteophytic new growth or the osteochondrotic or sclerotic proliferation round chronically arthritic joints merely appears where there is room for it. (The use of the word neurocentral as applied to Luschka's joints implies that it is a defect of union between centres of ossification, whereas it is a joint between the uncinate process of one vertebral body with the body above. I thought they were called the unco-vertebral joints)

Probably what their treatment has achieved is the relief of a group of restrictive joint lesions affecting the intervertebral joints of the fifth, sixth, and seventh cervical vertebræ. But one cannot be sure even of that, because the 14 lb traction would be palpably effective down to the third or fourth cervical vertebra. For example, it is quite possible that the traction whether the factor responsible is the richness of the food or the emotional impact of the *addition* If you smoke too much or if you refrain too strictly from smoking, if you are too busy or too idle, if, in fact, you do anything to disturb the anxious homœostasis of the bowel, however indirectly, retribution will descend It is a gastrointestinal purgatory, all that may be done is to regulate one's life in such a way that one may eventually pass through it to a higher state of being

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To listen to the atoms Red
In the face from stooping
He'd declare
The little devils
Artful as a barrel-load of protons
Full of mischief
Just put two of 'em together
And the consequences!
Sure
They'll save us all a heap of work
So long as we provide
The most exorbitant
Ideal conditions
But
The more I listen
More I feel that work
Is mankind's
Only hope

Letters to the Editor

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[1] Seale, J R *Lancet*, 1960, i, 1349

l the points showing the presence of detectable triiodothyro-
e activity were obtained by enzymic hydrolysis, while 60%
the points showing no detectable triiodothyronine activity
e obtained by alkaline hydrolysis However, Braasch et al,
heir table 3, describe an experiment in which the " column
dual " fraction of an enzymic hydrolysis was rehydrolysed
alkali This prolonged the minimum overall time to 116
urs and gave a triiodothyronine/thyroxine ratio of 0 14
own as ● in the figure)

These results are consistent with the existence of the error
tulated at the beginning of this note Inspection of the
tinent current literature reveals many papers to which the
ne criticism *might* be applicable but in which sufficient
ail to determine whether or not this is so has not been
plied

Please let me make this point clear A single possible
urce of error is pointed out in this note As examples of
ere this source of error may play a part, I have cited
pers which undeniably are worthwhile contributions in
eral respects Furthermore, there are many thyroid
periments performed with radioactive iodide which
uld not be affected by this error because of the presence
carrier iodide, short duration, or the ruling out of this
ect by proper controls

G W Carnrick Company,
Newark, New Jersey

MARSHALL E DEUTSCH

RADCLIFFE TRACHEOSTOMY TUBE

SIR,—It seems that, in one respect, Dr Sandiford
ug 27) has misread our article of Aug 20 Prototype A
acheostomy tube caused irritation, but when this was
placed by a tube *with identical measurements*, overdipped
latex (prototype B), the skin condition healed The
adcliffe tracheostomy tube has been available with
ms of two different lengths since 1956,[1] and for over
ighteen months has been made in three

Nuffield Department of Anæsthetics,
The Radcliffe Infirmary,
Oxford

R H SALT

CEREBRAL MANIFESTATIONS OF ADDISONIAN PERNICIOUS ANÆMIA

SIR,—Dr Fraser (Aug 27) has most ably described
problem which must be more common than is generally
ealised In 14 years of general practice in this area I
yself have come across three such cases

The first was a man of 54 who was admitted to a mental
ospital as a typical case of endogenous depression of many
onths' standing The correct blood diagnosis was made in
ospital and injections of 'Anahæmin' alone raised the
epression. He has kept well ever since and had regular
njections of vitamin B_{12}

The second was a case of depersonalisation in a woman of 43
She had in the first instance six months' treatment in a mental
ospital without any benefit Later at home she developed
xtreme pallor with an icteric tinge, and she was diagnosed as a
ase of pernicious anæmia at the general hospital Vitamin-B_{12}
njections have given her a normal blood picture, but her
nental state has remained just the same

The third case was a woman of 53 who was a depressed
liabetic. She had been in a state of depression for years
Pallor and paræsthesiæ developed and the local diabetic clinic
liagnosed pernicious anæmia with subacute combined
legeneration. She was given vitamin B_{12} and this cleared her
næmia, paræsthesiæ, and depression, and she has been
remarkably well ever since

In all three cases the mental symptoms developed long before the blood picture became obvious Under the circumstances it is fortunate that two out of the three made such a good recovery How long can pernicious anæmia lie latent? A friend of mine lost his father and his grandfather from pernicious anæmia. In middle age this man began to feel ill with intense lassitude and diarrhœa With such a family history his physicians must have looked for pernicious anæmia, but it was some four years before the blood-count revealed the true diagnosis He has been perfectly well since the institution of vitamin-B_{12} treatment.

All this makes one wonder how many more chronic cases in general practice are suffering from latent pernicious anæmia We are rightly advised not to give B_{12} until a precise diagnosis has been made, but the temptation to give some of these patients " a shot in the arm " is very real How accurate are the methods of early diagnosis advocated by Dr Fraser, and how soon will they be available to our patients?

Ibstock, Leicestershire.

C A H WATTS

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—The balanced and judicious comments by Dr Oliver (July 30) are indeed timely and deserve very careful consideration Those of us who have been privileged to gain our early experience in the most progressive mental hospitals, and have also acquired an eclectic psychiatric orientation—comprising individual and social psychological, as well as organic and physiological, concepts—and whose outlook is consequently far from " reactionary " or overcautious, have nevertheless all too often been faced, for various reasons, with the dilemma of steering a treacherous course between the Scylla of institutionalisation and the Charybdis of discharging prematurely our psychotic patients

The social and legal problems which confront us are apparent in the following statement[1]

" It is necessary to balance the possible benefits of treatment or training, the protection of the patient and of other persons, on the one hand, against the patient's loss of liberty on the other "—although in practice this is sometimes easier said than done, depending as it does on clinical judgment and experience, and too often also on administrative expediency It is no doubt true, as Professor Hargreaves[2] says, that those requiring compulsory detention are " a minority of about 20% of the patients who enter mental hospitals ", but it remains primarily the onerous responsibility of psychiatrists to ensure that these 20% are cared for in hospital as long as may be necessary, and that the community is also reasonably protected so far as some of these patients are concerned. Taking the figures for 1955, for England and Wales alone, 20% of admissions to mental hospitals still represent some 19,500 patients, and 20% of the mental hospital population, some 30,700 patients, and, in addition, it should be noted that, in 1954, second or subsequent admissions to mental hospitals were equivalent to approximately two-thirds of new admissions during the same year (63% for males, and 69% for females)[1]

It is of interest that the main points raised by Dr Oliver are emphasised in almost identical terms in a recent article by a French psychiatrist,[3] in which he draws attention to a large series of serious crimes of violence committed in France in the past few years by prematurely discharged mental patients (without, as the author observes, taking into account the numerous suicides and other tragedies attributable to this same cause) Many patients thus " sacrificed to administrative expediency " and the policy of rapid turnover are subsequently readmitted to hospital on a number of occasions, each time a little more deteriorated

Leconte concludes that the present situation, in France, appears to be " serious not only for public order and personal safety, but for the mental patients themselves who, when

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[1] *Lancet*, 1956, ii, 1247

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[1] Report of the Royal Commission on the Law relating to Mental Illness, pp 110, 310-311 Cmd. 169 H.M. Stationery Office, 1957

[2] Hargreaves, G R. Psychiatry and the Public Health, pp 113, 68-71 London, 1958

[3] Leconte, M *Ann Méd lég* 1960, 40, 246

relieved a lesion of the first costovertebral joints which are sometimes more important than the cervical intervertebral joints in the ætiology of pain in the upper limb, though I am not too sure why

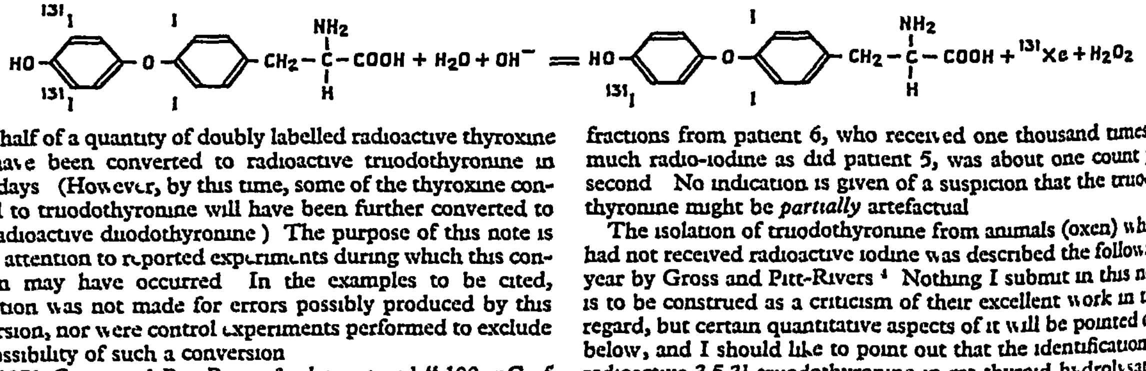
But the authors have left us without information on this It is a pity that they could not at least have described the objective consequences of the traction Have they at any time examined the amount of movement between individual vertebræ, or, more to the point, have they done so before and after treatment, so that they would know what they were doing? Almost all the things about which one would like to know more are the details of clinical examination When the pathology is in doubt, the clinical picture is the only source of information

Aberdeen DUNCAN TROUP

RADIOCHEMICAL SYNTHESIS OF TRIIODOTHYRONINE

SIR,—I should like to call attention to a correction which it might be necessary to apply to the results of certain published experiments performed with ^{131}I These are experiments of several days' duration performed with thyroxine labelled with large amounts of carrier-free ^{131}I under conditions such that some thyroxine molecules will be doubly labelled

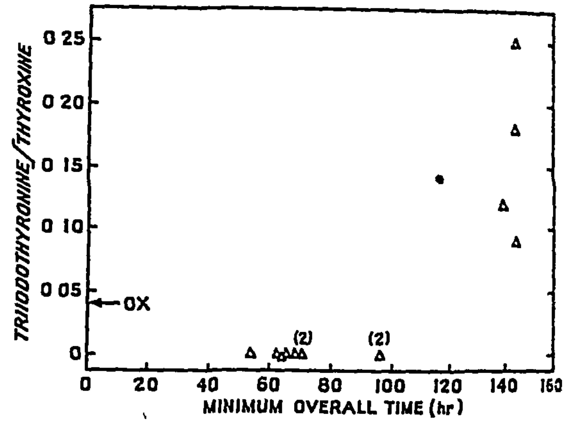
Radioactive decomposition of ^{131}I leaves an ^{131}Xe nucleus in place of the ^{131}I nucleus [1] Xenon cannot, of course, remain as part of the molecule which was a thyroxine molecule but will become detached, taking with it the orbital electron which had been supplied by the carbon to which its parent isotope had been attached The residuum of the thyroxine molecule will then have to react with a component or components of the solution in which it is dissolved A possible reaction is given by the equation



Thus half of a quantity of doubly labelled radioactive thyroxine will have been converted to radioactive triiodothyronine in eight days (However, by this time, some of the thyroxine converted to triiodothyronine will have been further converted to non-radioactive diiodothyronine) The purpose of this note is to call attention to reported experiments during which this conversion may have occurred In the examples to be cited, correction was not made for errors possibly produced by this conversion, nor were control experiments performed to exclude the possibility of such a conversion

In 1951 Gross and Pitt-Rivers [2] administered " 100 mC of Na ^{131}I " to each of six human subjects Since, in a subsequent paper,[3] these authors tabulate doses of radio-iodine as being either " mc " or " μc. ", one must conclude that this dosage of ^{131}I in the first paper was expressed in millicuries They chromatographed extracts of the blood-plasmas of these subjects and demonstrated two spots of unknown material concerning which they concluded " that the entry of radioactivity into unknown 1 roughly follows that of thyroxine, whereas that into unknown 2 follows that of radioactive iodide " No unknown 1 was detected until two days after the administration of ^{131}I

In a subsequent paper,[3] Gross and Pitt-Rivers identified unknown 1 as being triiodothyronine by means of two-dimensional and column chromatography In this paper they stated that " the possibility that triiodothyronine might be an artefact of the extraction procedure was eliminated by adding tracer amounts of synthetic radioactive thyroxine to plasma and analysing the mixture on the column, fig 2c shows that no triiodothyronine is formed under these conditions", but do not seem to have allowed time for the effect described above to be manifested They also state " That triiodothyronine may be a radiation artefact is unlikely for two reasons (1) it was detectable in the plasma of patient 5 who had received only 100 μc of radio-iodine, and (2) it has been isolated from the thyroid tissue of animals which had not received any radioactive iodine at all (unpublished) " No indication is given of the amount of triiodothyronine detectable in the plasma of patient 5, but it is perhaps noteworthy that the *peak* radioactivity of the column fractions from patient 6, who received one thousand times as much radio-iodine as did patient 5, was about one count per second No indication is given of a suspicion that the triiodothyronine might be *partially* artefactual



Δ indicates data from table 2 and ● indicates datum from table 3 of Braasch et al. Arrow indicates ratio of aminoacids obtained from non-radioactive ox thyroid by Gross and Pitt-Rivers Minimal overall time is that from administration of ^{131}I to determination of radioactivity in fractions and is in each case less than the actual duration by the time required for manipulations such as extraction and chromatography

The isolation of triiodothyronine from animals (oxen) which had not received radioactive iodine was described the following year by Gross and Pitt-Rivers [4] Nothing I submit in this note is to be construed as a criticism of their excellent work in this regard, but certain quantitative aspects of it will be pointed out below, and I should like to point out that the identification of radioactive 3,5,3ʹ-triiodothyronine in rat-thyroid hydrolysates, which they describe in the same paper, was performed on the thyroids of rats which had been given 100 microcuries of ^{131}I five days previously

Since quantitative data on the relative amounts of triiodothyronine and thyroxine will help in an evaluation of the likelihood of occurrence of the postulated artefact, let us examine the data of Braasch et al ,[5] who administered 0 3–0 5 millicuries of ^{131}I to humans and after 48 hours hydrolysed specimens of their thyroid glands and determined the amounts of radioactivity in different fractions of these hydrolysates according to a slight modification of the kieselguhr-column procedure of Gross and Pitt-Rivers In the accompanying figure I have plotted as Δ's the data of their table 2 (with the exception of two measurements they made on hydrolysates prepared in the presence of $Na_2S_2O_3$ and lacking triiodothyronine) The abscissa I have used is " minimal overall hours " or 18 plus the hydrolysis time, and the ordinates are the ratios of triiodothyronine radioactivity to thyroxine radioactivity The arrow at zero overall hours is the ratio of triiodothyronine to thyroxine as isolated from ox glands

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1 Friedlander, G , Perlman M L, Stehn, J R General Electric Chart of the Nuclides General Electric Research Laboratory, Schenectady, N Y
2 Gross J , Pitt Rivers R. *Lancet* 1951 ii, 766.
3 Gross, J , Pitt Rivers, R. *ibid* 1952, i 439
4 Gross J Pitt Rivers, R *Biochem J* 1953, 53, 645
5 Braasch, J W , Flock, E V , Albert, A *Endocrinology*, 1954, 55, 768

Neglected osteomyelitis remains a surgical disease, we gree, and removal of pus from the subperiosteal space is urely a matter of some urgency But it seems to us more nportant to recognise that diagnosis within the first orty-eight hours, and immediate transfer to hospital as an nergency, offers a very good chance of avoiding all that, nd of achieving rapid healing with return to full activity a matter of weeks

The Childrens Clinic,
Royal Victoria Infirmary,
Newcastle upon Tyne.

A E Bremner
G A Neligan

MEDICAL SERVICES IN SOUTHERN RHODESIA

Sir,—The contribution of Dr Stott (Aug 27) to The Vider World has aroused my nostalgia I spent a year in ractice in Southern Rhodesia as a young graduate I ave never regretted this sojourn, and I have often egretted my failure to settle permanently in Rhodesia am glad to learn that there are still opportunities there or *the adventurous young man, and I commend* Dr tott's suggestion that service in Southern Rhodesia vould represent a real contribution to better race relations t would be interesting to have some idea of the numbers of African doctors who have been recruited up to now, and he numbers who may become available over the next ten ears or so There is perhaps a tendency to exaggerate he size of the possible reinforcement The letter of Professor Davies (Aug 27) draws attention to a similar ield for over-estimation

St Mary's Hospitals
for Women and Children,
Manchester

W I C Morris

EXPIRED-AIR RESUSCITATION

Sir,—Since you published my letter in May,[1] describing regurgitation after the application of the mouth-to-mouth method of artificial respiration, a colleague of mine has had a similar experience

He was called to a collapsed patient who had ceased breathing and whose pulse was scarcely perceptible He used mouth-to-mouth resuscitation for some minutes—perforce intermittently because of the need to clear the mouth of regurgitated vomitus He turned the patient on to his chest and continued with the Holger-Nielsen method The patient died despite his efforts My colleague was quite revolted by the task he set himself and considers the regurgitation, quite apart from its intrinsic danger, a severe æsthetic drawback to this method

I was myself present recently at the revival of a 19-stone man who had been overcome by hydrocarbon vapour in a ship's tank, and with delay and difficulty rescued Holger-Nielsen artificial respiration was performed with the eventual recovery of the victim He was for some time blind after the event, which would indicate a severe degree of cerebral damage, fortunately reversible The efficacy of the Holger-Nielsen method, under field conditions, is particularly well shown

On the strength of my own knowledge of the effect on the stomach of mouth-to-mouth resuscitation, I would not now use it until I was convinced that regurgitant vomitus in the oropharynx is of no consequence to an apnœic person

It seems likely that peak pressures achieved by this method overcome the resistance of the cardiac sphincter and cause the regurgitation Mouth-to-nose breathing, advocated by Dr Henning Ruben,[2] would appear to overcome this objection

Medical Department,
Esso Refinery,
Fawley, Southampton

G Matthews

VALUE OF A LARGE DOSE OF ANTITOXIN IN CLINICAL TETANUS

Sir,—The paper of July 30 by Professor Brown and his colleagues suggests that Jamaican children were included in the clinical trial In fact neither I nor my pædiatric colleagues in Jamaica considered it justifiable to withhold antitoxin from our patients with tetanus, because we were firmly convinced of its value

At the University College Hospital of the West Indies few cases of tetanus are seen and the experience of the disease is far less than in Ibadan The standard treatment is 100,000 units of antitoxin for neonates and 200,000 units for other children, half the dose being usually given intravenously Sedation is achieved by chlorpromazine and phenobarbitone, the dosage being carefully controlled according to the clinical condition of the patient

During the past five years 27 cases of tetanus have been treated in the children's ward of whom 10 died 5 out of 8 cases of tetanus neonatorum died, if these are excluded the mortality of children is 5 out of 19 The mortality of 26% in this small series compares with 49% for Brown et al 's patients treated with antitoxin and 76% for those not treated with antitoxin I should like to pay particular tribute to the house-officers and nursing staff of the University College Hospital whose devoted care enabled so many of the children to survive

University College Hospital of The West Indies,
Mona, St Andrew, Jamaica

E H Back

HYDROCORTISONE BY INHALATION

Sir,—I was interested by the paper in your issue of Aug 20 by Dr Langlands and Dr McNeill, in which they report the absence of any improvement, as regards respiratory function tests, in 10 patients with chronic asthma, when treated with hydrocortisone-acetate inhalations for a month I agree that the results of this therapy in chronic asthmatics are often disappointing, but I do not think it is necessary to conclude from this investigation that hydrocortisone inhalations are of no value, and have no place in the treatment of asthma

10 patients is a small number from which to draw definite conclusions, and they appear to have been an unfavourable group having suffered from asthma for periods of between 12 and 26 years, some having emphysema, and 4 having $^1/_2$ oz of sputum daily In spite of this, 4 patients had subjective improvement on the hydrocortisone and only 1 on the placebo, which is about the relative proportion I would expect in this group I do not think it need be concluded that this subjective improvement was necessarily a chance finding or due to the " tonic " effect of the inhalation of 15 mg of hydrocortisone daily (perhaps half being absorbed), simply because the respiratory function tests estimated once or twice a week showed no parallel improvement The patients, no doubt, assessed their symptoms throughout the 24 hours of every day of treatment and possibly some were especially liable to nocturnal attacks of wheezing Brockbank and Pengelley[1] obtained significant results in a double-blind controlled trial using extremely small doses, which surely eliminates the " tonic " effect as a substantial factor I agree that respiratory function tests may be very valuable in assessing the results of treatment in chronic asthma but I do not think they are always necessary or justifiable in acute asthma Some of our patients[2] were experiencing fairly severe continuous asthma during the trial, and the response to hydrocortisone as opposed to the placebo, and also to routine antispasmodics, &c , was sometimes dramatic and incontrovertible

I have come to use hydrocortisone powder inhalations infrequently for asthmatic patients, not because they have no effect but because they are usually much less effective than systemic corticosteroid drugs, the dangers of which would

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[1] *Lancet*, 1960 i, 1070
[2] Ruben, A., Elam, J O , Ruben, H *Brit* [illegible] 1959, ii, 69

[1] Brockbank W , Pengelley, C D R *Lancet*, 1958, i, 187
[2] [illegible], W H , Heyworth, F *Brit med J* 1958, ii, 768

[illegible] Medical College

really cured, will once again see closing before them the doors which were beginning to open, but which one has no right to open forcibly, or surreptitiously "

There is undoubtedly a need for reappraisal of the clinical and administrative criteria for discharge (on trial or otherwise) of psychotic patients from mental hospitals, combined with an objective, statistically representative, follow-up survey of such patients Most important of all, at the present time, is the lack of continuity of the treatment in hospital of the psychiatric patient, and subsequent provision, so far as it may exist, for his "aftercare" As Hargreaves[2] states, "on discharge from hospital, the patient's aftercare, resettlement, and rehabilitation was made a function of the local authority by the same Act which removed from it the administration of the mental hospitals This function was not made an obligation of the local authority Small wonder that this aspect should have been largely neglected How can continuity of care be provided for the psychiatric patient with such a division of responsibilities between authorities whose boundaries bear no relationship to each other?"

As, for example, in the case of psychiatric reports for juvenile courts, it is not only useless but also highly detrimental to the patient and society alike to make recommendations that cannot, in practice, be implemented, and it is futile and potentially dangerous to take for granted, for reasons of administrative expediency divorced from clinical judgment, the existence, magnitude, and efficiency of services and facilities that are, for the most part, not in fact available, and for which, indeed, apart from the many other obstacles, there is such a deplorable lack of adequately trained, specialised personnel

Bransgore, Hampshire R H AHRENFELDT

OCCAM'S RAZOR

SIR,—Your interesting annotation of Aug 6 mentions that the learned inaccuracy *Entia non sunt multiplicanda praeter necessitatem* is still given in a vast transatlantic publication It is, perhaps, worth noting that it is also still given in the *Oxford Book of Quotations*

Kingsdown, Deal, Kent. W B ROANTREE

OUR POOR THAMES

SIR,—Mr Longmore and Dr Thompson's conclusions (Aug 20) refer to a part of the river considerably nearer to the mouth than the districts of which I am M O H, nevertheless I have had samples as polluted as theirs without being able to convince myself that the river could on that account "constitute a major menace to public health" On the contrary I have recently advised one of my councils in the following terms

> "Although no one can guarantee that no case of infectious disease could ever occur through river bathing, the risk is in my view infinitesimal, certainly no greater than that of being knocked down crossing the street or of getting food poisoning any time one buys food in the open market Finally, although I have been for nearly fourteen years a Medical Officer of Health of riverside authorities with bathing places, I have never known any case of illness attributable to bathing in the river, and in my view the pleasure and healthful effects of bathing very far outweigh any risk involved"

I have spoken to many doctors, but I have yet to find one who can quote me a single case of typhoid, poliomyelitis, or even Weil's disease which could reasonably be presumed to have its origin in the ingestion of river water Can Mr Longmore or Dr Thompson produce any such evidence?

The pollution of sea beaches which touched off their alarm is, everyone agrees, revolting and inexcusable from the amenity point of view, yet no one, so far as I know, has been willing to come forward and say it constitutes a public-health risk.

There are so many graver dangers which an M.O.H. must bring to the notice of the inhabitants of his area that he should, I feel, be most careful in crying wolf over remote and theoretical possibilities

Oxford

HECTOR MACKENZIE-WINTLE
Medical Officer of Health,
South Oxfordshire Combined District

UNITS

SIR,—May I plead for uniformity in the use of units? In a recent paper the fluid balance of a patient was quoted as (*a*) pints intake and (*b*) millilitres urinary output. In *The Lancet* of Sept 3 (p 527) I am introduced to a unit with which I am unfamiliar, the square foot-millimetre, to designate the area of a dialysing surface. If you think that we should still measure things in minims, fluid ounces, and pints, grains, scruples, and ounces, inches and feet, I shall respect your opinion However, having been brought up as a scientist, I find these units irrational and so expensive in calculating time that, in company with European colleagues, I am sometimes discouraged from trying to understand publications which employ them

Department of Biochemistry,
The Royal Infirmary,
Glasgow

JAS C EATON

ACUTE HÆMATOGENOUS OSTEOMYELITIS

SIR,—That early diagnosis and an effective antibiotic, in effective dosage, would render any form of surgical operation unnecessary in some cases of acute hæmatogenous osteomyelitis, was prophesied by Florey and Florey[1] 17 years ago The conditions under which this prophecy could be fulfilled were defined in pathological terms by Trueta and Agerholm[2] 12 years ago But this important possibility has been either doubted or not seriously discussed in two recent editorial comments[3,4] on the treatment of the disease

Having seen many cases in which the Floreys' prophecy has been fulfilled in practice, we have attempted to define[5] in clinical terms the conditions under which such a result could be expected Even in the severe form of the disease we found that 9 out of every 10 patients whose treatment with an effective antibiotic in adequate dosage was started within forty-eight hours after the onset of the pain showed rapid and complete healing without any form of operation whereas pus had to be removed surgically (by aspiration or by open operation) in 6 out of every 7 cases whose effective antibiotic treatment was started after the first forty-eight hours Also, serious complications, such as septic arthritis, were almost confined to the late cases

The first forty-eight hours after the onset of the pain therefore seems to be of crucial importance We regard it as the target period within which the family doctor should aim to make the correct diagnosis (or suspect it), and refer the patient to hospital, where he can be adequately investigated, treated with antibiotics in adequate dosage (e g, injection every three hours initially), and operated upon if this should after all prove necessary We know that about three-quarters of the patients whom we see here have sought medical advice within the critical first forty-eight hours, and we are most grateful to the many family doctors whose prompt actions have made it possible for us to see the Floreys' prophecy so often fulfilled. Their patients have good reason to be grateful to them too

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1 Florey, M. E., Florey, H W *Lancet* 1943 i, 387
2 Trueta, J, Agerholm, M *Post Grad. med J* 1948, 24, 229
3 *Brit med J* 1960 i 537
4 *Lancet*, Aug 20, 1960 p 415
5 Bremner, A E., Neligan, G A Recent Advances in Pædiatrics (edited by D Gairdner), chapter 13, p 364 London, 1958

l. She recovered from her coma after 3 days and entered a orous state which lasted some 6 or 7 days, during which e she was hardly cooperative, though only drowsy When y recovered this patient had complete amnesia for the period ending from 72 hours before admission to 9–10 days after mission—i e , for the entire duration of stupor and coma

The outstanding feature of both these cases was the ntity of clinical state between these patients and those in rbiturate coma and the absence of the dramatic recovery at one would usually expect in any case of hypoglymia treated adequately with parenteral glucose solutions

'oisons Unit, Oldchurch Hospital,
Romford, Essex
S Locket
I P Brown

STERILISATION OF THE DIABETIC'S SYRINGE

Sir,—Must it be sterile? My experience dates from 26 and for many years now I have kept the assembled ringe and needle dry in a vulcanite case

I pull the plunger out to the required mark, push the needle rough the untreated rubber cap, withdraw the insulin, and ject it I blow out with the plunger any remaining drop, and ut the assembled syringe and needle back into the vulcanite ntainer All this takes about 60 seconds I do not touch e needle except at the hilt to hold it firm, and I have long ago scarded the metal top of the syringe

When a bruise appears at the site of injection after many onths, I have a new needle Apart from this there is no sign sible to the naked eye that injections have ever been made, nd not the slightest infection has arisen.

A year or two I drew the distal end of the needle in use over culture-plate, a rich growth of *Staphylococcus aureus* eveloped. One must be immune to one's own staphylococci

Hove. G M Wauchope

HYPOKALÆMIA, CARCINOMA, AND CUSHING'S SYNDROME

Sir,—I read Dr Bagshawe's article of Aug 6 with nterest in view of a patient who was recently in this ospital and whose diagnosis at the time of his first dmission gave rise to considerable discussion because of he unusual association of some of the features of ushing's syndrome with low serum-potassium and nexplained œdema

A man, aged 60, in July, 1956, first attended hospital aving had two months' swelling of the ankles No renal, utritional, or cardiac cause was found to explain this July, 957 recurrence of œdema not now disappearing on bed rest, gain no cause found. January, 1958 first noticed bruising of kin and œdema became worse

July, 1958 admitted to hospital under Dr E R Cullinan Looked well. Fundi normal Soft right axillary node palpable, otherwise no lymphadenopathy Pulse 76, regular Blood-pressure 175/90 mm. Hg No cardiac enlargement. Abdomen obese. Liver, spleen, and kidneys not palpable No other mass Central nervous system normal. Skin showed (*a*) purpuric spots and patches over trunk and arms, (*b*) some small pigmented papillomata, (*c*) a few Campbell de Morgan spots, and (*d*) some flat pale brown plaques over chest.

Hæmoglobin 82% White blood count 8400 per c.mm Platelets 161,000 per c.mm.

Serum-proteins total 5 1 (albumin 3 8, globulin 1 3) g per 100 ml Serum-sodium 146 mEq per litre Serum-potassium 2 8 mEq per litre Serum-chlorides 101 mEq per litre

Glucose-tolerance curve diabetic in type

Basal metabolic-rate −8%

24-hour urine specimen 17-ketosteroids 15 0 mg per day, 17-hydroxycorticoids 37 6 mg per day The amount of beta-17-ketosteroid excreted was within lower limits of normal range

Calcium excretion 495 mg per 24 hours (normal 120–270 mg per 24 hours)

Chest X-ray showed fractures of right 5th and 6th ribs, and rather thickened costochondral junctions

X-ray lumbar spine showed compression collapse of D12

Erythrocyte-sedimentation rate 2 mm. in one hour

A presacral air insufflation was attempted but was unsuccessful because he was unable to walk owing to D12 collapse

Corticotrophin was given and the 17-ketosteroids rose to 24 mg on the fourth day and 17-hydroxycorticoids rose to 92 5 mg on the fourth day

These investigations showed that he had some of the features of Cushing's syndrome

(1) Osteoporosis with spontaneous fracture
(2) Diabetes mellitus
(3) Purpura
(4) Increased adrenal steroid output

In addition, he had a low serum-potassium and a high serum-sodium

A diagnosis was made of adrenal hyperplasia, and in view of his deteriorating general condition the adrenals were explored on Oct 24, 1958 They were moderately enlarged The whole of the left adrenal was removed and four-fifths of the right. Histological section showed the changes of Cushing's syndrome, there was no hypertrophy of the zona glomerulosa to suggest Conn's syndrome

Postoperatively his œdema rapidly disappeared and it was then obvious that his muscles were extremely wasted and he was unable even to lift his leg up from the bed Subsequent progress and investigation showed him to be in positive nitrogen balance and in normal calcium and potassium balance He was given testosterone, and a maintenance dose of cortisone 12 5 mg b d was reached by Nov 28

On Dec. 12 he developed pneumonia (after a prevalent influenza epidemic) and after twenty-four hours suddenly collapsed, his blood-pressure falling to 70/20 This was considered to be an adrenal crisis and responded only to hydrocortisone in combination with noradrenaline. He rapidly recovered from a state of collapse but since that time a return of his œdema had been noticed, serum chemistry remained normal, and diuretics had moderate response At the time of discharge there was no evidence of diabetes, but œdema of the ankles and hands was still present. He was able to walk with a spinal corset and sticks

His condition remained much the same until May 11, 1959, when he noticed intermittent central abdominal pain This persisted for two weeks and on May 25, 1959, he was admitted with severe abdominal pain in a state of collapse A diagnosis was made of intestinal obstruction, but he was not fit for surgery and he then perforated Serum-sodium 145 mEq and serum-potassium 3 7 mEq at this time In spite of rigorous therapy he did not improve and died on June 7, 1959

Necropsy (Dr A. G Stansfeld)—The body was well-nourished, though the state of nutrition was partly masked by gross subcutaneous œdema affecting not only the lower limbs but the trunk and upper limbs There was marked muscular wasting of the peripheral limb muscles but abundant subcutaneous fat over the trunk.

Abdomen Diverticulitis of colon One diverticulum in ascending colon had perforated. Suppurative peritonitis with abscess in lower abdominal cavity

Liver 2770 g Multiple secondary nodules of carcinoma

Neck enlarged nodes in both supraclavicular fossæ, large node replaced by growth in right paratracheal region

Remaining portion of right adrenal had undergone hyperplasia, weight now 7 5 g

Section of the paratracheal node showed a highly cellular and clearly malignant neoplasm Most parts of the growth lacked distinctive features, but the appearances of the tumour favoured the supposition that it was a primary neuroblastoma arising from the sympathetic chain at the thoracic inlet Sections of the liver showed numerous metastatic deposits of a cellular malignant neoplasm resembling the growth in the neck. (Examination of the head and brain was not permitted.) The adrenalectomy was done through a posterior approach and so it is impossible to say whether liver metastases were present then or not

If the neuroblastoma is to be considered the cause of the adrenal manifestations then he must have had this for over three years before death, and yet there was no involvement of the adrenals themselves with growth.

St. Bartholomew's Hospital,
London, E.C.1
J A Parrish

Obituary

GORDON GORDON-TAYLOR

K B E , C B , M A Aberd , M S , B Sc Lond , LL D , Sc D ,
F R C S , F R A C S , F A C S

THOUGH he had become almost a legendary figure, Sir Gordon Gordon-Taylor at 82 was still very much part of the medical scene, and the news of his death on Sept 3 will bring real regret to the many people all over the world who liked and admired him so much One of the most brilliant surgeons of his day, he became in later years a spokesman and ambassador of British surgery He was still, as always, both a stimulus and a support for younger men, and indefatigable in his help to Commonwealth and foreign students visiting this country

Central Press Photos Ltd

Gordon-Taylor was born in Aberdeen and was educated at Gordon's College and the University, where he graduated in arts in 1898 The same year he moved south and entered the Middlesex Hospital with a scholarship Having qualified in 1903, he became demonstrator in anatomy under Peter Thompson, and in that year, when the University of London instituted an honours degree in anatomy (B SC) he and Victor Bonney were the first candidates They worked long hours into the night, heating coffee essence on a bunsen burner to sustain them, and attained first-class honours This interest in anatomy he retained all his life, and he continued to add to his qualifications by gaining the M S Lond and the F R C S in 1906 In the following year, at the age of 29, he was elected to the staff of the Middlesex Hospital as an assistant surgeon

It was round the Middlesex Hospital that most of Gordon-Taylor's work centred He served other hospitals too, including for a time the Royal Northern, but the Middlesex was his home He was assistant to Pearce Gould, and to Bland-Sutton who influenced his early career, and by the outbreak of the 1914–18 war he was recognised as an established and very able surgeon During this war he served in casualty-clearing stations, gaining great insight and experience in major abdominal surgery, and was appointed consultant to the 4th Army

On his return to the Middlesex he brought back many ideas —such as the use of blood-transfusions, given in those days with a Kimpton tube—which enabled him to develop and expand the scope of his surgery In 1920, on Bland-Sutton's retirement, he became full surgeon to the hospital and undertook one of the busiest practices in London At the Middlesex he operated on three afternoons a week—including Saturdays, so that foreign visitors from abroad need not feel that British surgery had adopted a weekend attitude! During the '20s and '30s he worked and wrote on many aspects of surgery Many of them were connected with cancer—of tongue, breast, colon, and stomach, others were more general, such as parathyroid and carotid-body tumours But two of his great subjects were reserved for later years—innominate aneurysm, published when he was 72, and hindquarter amputations, which he carried out in the years of his so-called retirement His hundredth was successfully performed when he was 80

From the outbreak of the late war Gordon-Taylor served in the Royal Navy with the rank of surgeon rear-admiral His territory covered south-east England, and in the period of air-raids he was actively operating and advising on casualty work His former experience with war injuries was invaluable, but he was one of the first to modify his approach in th of changing conditions His duties involved travelling he visited many countries during the war years He was of the group of surgeons who visited Russia and con diplomas of the Royal College on Russian colleagues Pacific Fleet saw him in 1945

His time at the Middlesex was up before the end of th but for Gordon-Taylor retirement was a misnomer It the start of a new phase of his surgical activities Act mind and body, he continued to dazzle friends and asso by his operative skill, while in public life more and demands were made on him as teacher and speaker He lect in many places—Cairo and Toronto, Leeds and C Harvard and Melbourne, Athens and Munich, Lahor Edinburgh He acted twice as professor of surgery in Peter Bent Brigham Hospital and as a postgraduate pro in Cairo He was president of the Association of Surgeons the Royal Society of Medicine, and of Medical Society of London Surgeons France, Belgium, Greece, Germany, N way, and Denmark welcomed him honour The United States accorded the distinction of commander in the Leg of Merit He examined in many coun and universities, but what he p liked best was examining in anatomy the primary F R C S , which in one way another he undertook for many years

The Royal College of Surgeons was abiding interest He was elected to council in 1932 and was vice-preside 1941–43 Three Hunterian professor were accorded him, and as vice-dean of Institute of Basic Medical Sciences he counsellor to the young visiting sur until the day of his death His Brad lecture and two Vicary lectures at college were memorable occasions was an honorary fellow of the colleges surgeons of Australasia, America, Can Ireland, and Edinburgh, an hono member of the surgical societies Belgium, Norway, Greece, France, and Germany, and a honorary graduate of the universities of Toronto, Athe Melbourne, and Cambridge Of these distinctions two, pe haps, gave him particular pleasure—the doctorate of sc given to him at Cambridge by his old friend Lionel Wh and the fellowship of the surgical college of his native l The gold medal of the Royal Society of Medicine was unique distinction that he received recently, and signal hono were bestowed on him by the *British Journal of Sur* through an appreciation in 1919 and a special number on 80th birthday At this time his attitude to these tributes wa expressed by his remark that " the kindness of myriads friends has helped to make my entry into the eighties less and depressing than I had anticipated "

As a surgeon he was an acknowledged master

" No man could have been as good as Gordon was on day," writes T H S " His gentle handling and abili know where he was and what he was doing, in days wh anæsthetics and other aids to surgery were only partly de oped, was little short of miraculous He was most at hom the abdomen and neck, less happy with bone work, frankly declined to touch cerebral surgery He pione thoracotomy in his early endeavours to treat cancer of œsophagus, and in the full generosity of the man he pro every opportunity for his assistants to develop a spec even though he saw in this fragmentation the end of the of the true general surgeon He taught by example and encouragement, he rarely criticised, but was unfor carelessness or slackness He never forgot a pupil and w do everything that he could do to help them in their And it was not only his personal pupils he helped, d, and many did, seek his advice, which he gave in full sure. Generosity such as his has rarely been found."

W once described work with Gordon-Taylor as "a derful education for a young and inexperienced house-geon, for he expected one to take a share in all that was g on and one's work was not limited to holding retractors swabbing-up blood. He too regarded patients as human gs and he never gave up while there was the remotest nce of a successful issue to a case"

s a speaker and lecturer he was in a class by himself always said that his addresses took long preparation, they gave an impression of spontaneity His rounded se stopped just short of the florid, and his delivery had hythm and force that made the speech as well as its stance a joy to listen to—and the more memorable ause such oratory can now be heard so rarely It was same with his writing he took immense care in paration, polishing and repolishing He wrote two nographs, the *Abdominal Injuries of Warfare* and *The amatic in Surgery*, and with Prof Charles Wells a graphy of Charles Bell which was only recently mpleted.

Outside surgery his acknowledged interests were few was a classical scholar and had been chairman of Horatian Society He was a devotee of good cricket, d when not otherwise occupied was to be seen in the ernoons at Lord's—outside which he met the accident ich caused his death. His other relaxation, one might y, was walking, and to maintain physical fitness he alked several miles each day He was also an excellent llroom dancer and used to spend evenings after a long erating list in this way, and arrive at the Middlesex in e small hours to see how the patients operated on were rogressing His mode of life was selective, his habits stemious He was, for all practical purposes, a non-noker, and he ate and drank little He had never, he id, been in a public house or inside a cinema, and had nly seen television when it related to surgery His olidays were irregular and rare—a few days walking n his beloved Highlands or a day in bed reading the lassics in an Edinburgh hotel Occasionally he visited ontinental clinics to study some particular interest, and n these occasions he often took as his guests his anæs-etist and assistants After the war he was a much more avelled man, and international airlines knew him well istance meant little to him and he would willingly visit nother continent for a few days if so requested He ould not refuse an invitation, however inconvenient, if t was to help British surgery

His appearance and attire did not vary with the years, nd the Harley Street area could recognise from afar the lim, alert, and dapper figure striding along coatless and with head just a little on one side Always carefully dressed, he wore consistently a wing collar and bow tie, but his most characteristic foible was a carnation which was present winter and summer, at home or abroad His voice was easy and charming. it never directly suggested the Scots ancestry of which he was so proud, but he was at all times fond of the Northern idiom

"But the main characteristic of the man", as T H S says, "was the friendship and loyalty that he evoked in everyone he met When he made a friend he kept him, and each year hundreds of Christmas cards written in his own hand went out to people all over the world

"It was not easy to know him intimately, there was a reserve beyond which only a few could penetrate to read his inmost thoughts Surgery and all that it meant was open to everyone, as also were his hobbies of cricket and the classics, but apart from that there was only an occasional glimpse of the man—possibly afraid to reveal his generosity and sympathy for humanity in a modern age that he did not appreciate. Honours and applause meant less to him than the achievement of good surgery in relieving a fellow man's suffering One of his great friends wrote of him as the most erudite of modern surgeons, as well as in his time the prince of craftsmen and (greatest of compliments) the 'doctor's surgeon'"

Another of his old house-surgeons, R S H, writes again of the devotion he inspired

"He induced us to put forth a little more than our maximum effort, not by driving us, but by convincing us that the only activity in life which really mattered was surgery He was kind to us in big and little ways He supported us in our subsequent careers with a bias, a passion, and an energy which, in the end made the majority of us consultants He was only once heard to make a slighting remark about a former house-surgeon—'he was not a good house-surgeon he put on weight while he was with me' He gave us a cystoscope and gold cuff-links at the end of our tenure of office He paid us for helping him in private on so princely a scale that we, the unpaid house-surgeons of those days, could on the rare occasion of a free evening emulate our chief by going to the Savoy to dance He told us stories of surgeons, of patients, of quaint events in his inimitable manner He secretly provided comfort or convalescence for hospital patients, and we found out only by chance He was a fabulous figure, and we copied his surgery and his gestures, his tricks of technique, and his mode of speech. We shall no longer receive little congratulatory notes on our small triumphs or hear some delightful anecdotes at a corner of Harley Street, but we shall remember G G-T to the end of our days and carry in our surgical substance things which he planted in us"

Gordon-Taylor was created K.B E. in 1946 Lady Gordon-Taylor, whom he married in 1920, was Florence Mary Pegrume, F.R.S.A. She died in 1949, and they had no children.

ALAN FILMER ROOK

K.B E, C.B, F.R.C.P, D P H

Air Vice-Marshal Sir Alan Rook, whose death on Aug 26 we announced last week, had made in both his medical careers—one in the Royal Air Force and the other at the University of Cambridge—a notable contribution to the health services of young people He had great experience of the problems of young men and women under stress, and his sincerity and honesty inspired their confidence

He was born at Forest Hill in 1892 and was educated at Mill Hill School and Guy's Hospital A contemporary remembers him as a modest and gentle unassuming man who "was liked by everyone and was good at everything" After qualifying in 1915 he joined the R.A.M C and at the end of the war, after a brief period of postgraduate study at Guy's, he joined the R.A.F

In 1922 he took part in a sandfly-fever investigation in the Middle East, and three years later he was posted to the Palestine General Hospital as medical officer with the rank of squadron-leader Later he was transferred to Iraq and in due course became deputy principal medical officer On his return to England in 1928 he spent some time in the R.A F pathological laboratory at Halton, and in 1936 he was appointed consultant in medicine at the Central Medical Establishment Of Rook's work in the Service C P. S writes

"During the earlier years there was not enough to exercise his eager and active mind, but when before the second war he became consulting physician at the Central Medical Establishment he found what he had long desired, scope for his clinical ability and interests, with able colleagues and excellent facilities for investigation The war brought him further opportunity and full recognition of his talents He enjoyed working with other consultants of his own calibre and teaching them to apply their knowledge to Service problems, and they in turn appreciated his skill as a physician and his worth as a friend "

Rook was appointed C B in 1946 and K B E in 1948 He was elected F R C P in 1939

He retired from the R A F in 1948 at the time when the University of Cambridge was starting a student health service, and Sir Lionel Whitby invited him to take charge of it The new venture began in a hut at the back of Downing College, but some ten years later it moved to a new building at Fenners, with consulting-rooms, X-ray department, physiology room, and gymnasiums In that time Rook devoted himself entirely to the health and welfare of Cambridge men and women, and he saw their problems gradually change, as physical disabilities—especially pulmonary tuberculosis—declined, while psychological problems became more important After his retirement, two years ago, he stayed in the department to analyse the 15,000 case-records which had passed through his hands, but his long illness unfortunately interrupted his proposed correlation of academic performance, physical prowess, and mental stability

A L B writes

" Shy and sensitive, with warm emotional reactions, Rook never succeeded fully in adapting himself to the critical Cambridge atmosphere More than once it fell to me to fire the bullets that he manufactured because he could not trust himself to reply calmly on a matter about which he felt strongly Perhaps his greatest contribution in Cambridge was the encouragement of the spirit of adventure in the young With the approach of each long vacation the upper floor of our building at Fenners became strewn with first-aid kits for undergraduate expeditions, and he supplemented these with personal advice to each team Characteristically he decided that one expedition was going to so remote a place that it must be supplied with morphine, and it became necessary to prolong the subsequent official correspondence until such time as the expedition returned, fortunately with the morphine untouched

" Another activity to which he gave much time was the building up of an organisation whereby tuberculous students could continue their studies while under treatment The rehabilitation of athletes after injury was another of his interests As time went on his advice came to be sought on an extraordinary range of problems at all levels within the university He was the sort of man that it is impossible to replace, for his niche is carved in the affections Everyone respected Rook They also liked him "

He is survived by his second wife, formerly Elizabeth Wilson, whom he married in 1946

JAMES RUSSELL

C B E., M.B Glasg, F R.C S E., F R.F P S

Mr Russell, consulting surgeon to the Victoria Infirmary, Glasgow, died at his home at Newton Mearns on Aug 26 at the age of 78 He was a pioneer of orthopædic surgery in the West of Scotland, and it was largely through his efforts that the Philipshill Hospital at Busby was set up as an orthopædic annexe of the Victoria Infirmary

After qualifying from the University of Glasgow in 1902 he held a number of house-appointments at the Victoria Infirmary, where eventually he was appointed visiting surgeon His work to establish orthopædics as a specialty began during the 1914–18 war, and during the late war he was surgical director of the Western Scotland civil defence area He helped to organise the emergency hospitals at Killearn, Ballochmyle, and Law At Ballochmyle he started a jaw injury and plastic surgery unit He was appointed C.B E in 1945 Three years later he retired from his hospital appointments, but he served as a member of the management committee of the Victoria hospital group

A colleague, who first met Mr Russell in 19 1938 when he was recruiting staff for the new fr clinic and orthopædic department which a year later he " imposed " on the Victoria Infirmary, wr

" His enthusiasm for his new creation was bound his ability to get his way amazing He seemed to p indirect to the direct approach, but he knew where he going and usually got there He was a most staunch su of his staff and stuck up for their rights strenuously, personally found that despite a serious and, at th apparently bitter disagreement his friendship was not drawn In fact later it increased and perhaps our diff was partly the reason, for if there was one quality he and showed, it was a sturdy independence He could not conceit and was constant in his criticism of bureaucra bureaucrats, with whom he always enjoyed a battle—som carrying in his pocket letters to them which he would out and read aloud They were never posted, but I s that they relieved his feelings, and probably the amm they contained got to the targets in the end He was in a hurry and even while still busy with work had tim long talks over cups of tea, playing havoc with the arrang and plans of his impatient juniors But for the patient lis it was never time wasted, for there was always a lesson in he said—and at any rate it taught us the value of time talk was allusive and not always easy to follow, but it full of homely phrases and often clear enough, as wh told us that someone was ' no thinkin' right ' or ' no stable, that yin ' He was not understood or appreciated everyone, but his friends believe that he did a treme work and by them he will be sadly missed "

Mr Russell is survived by a son and a daughter

Dr JONES-DAVIES

A colleague writes

Dr Jones-Davies' chief personal qualities were loy against any odds to all those with whom he came in con and humanity " Each man is of importance to himself " one of his favourite quotations, and he always bore this in m in his work He had great tact, and when I was seriously under his care he visited me daily without giving me t slightest inkling of the situation His overall grasp of a m case has helped us all to the wisest course many times He a lovable nature and a warm heart, and not seldom showed really poetic turn of phrase

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Appointments

ANTON, H C., M.B Aberd, D M R D radiologist (S.H.M O), Aber General Hospital and Aberdeen special hospitals
BUCHANAN, JESSIE R G, M B Edin part time S.H.M.O, departm venereology, General Infirmary, Leeds
CAPON, MARGARET, M B Lond assistant M O and school M.O, Northam tonshire
DAVIES, D M, M.R.C P S H.M O in charge of the receiving room, L Hospital
GRUENEBERG, R. H K, M D Basle, F R C.S senior casualty officer, Kirk General Hospital
LAVERICK, R C, M B Leeds, D P H deputy M.O H, Halifax
LOCKEY, EUNICE, M D, B SC Lond consultant pathologist, Royal Ma Hospital, London
MANNING, L K, M B Lond, M R C.P E assistant chest physician, Ches field and North Derbyshire area
MCCOMB, T N, M B Glasg assistant anæsthetist, Ballochmyle Hos Mauchline, Ayrshire
OKOLSKI, STEFAN, M.B Polish Sch Med Edin senior casualty Wansbeck group of hospitals
THOMPSON, B A, M B Edin, F R C.S.E. consultant surgeon, Sc Borders Hospitals board of management

The Hospital for Sick Children, Great Ormond Stre London:

ATWELL, J D, M.B Leeds, F R C.S surgical registrar
DUDGEON, J A, M C., M.D Cantab consultant pathologist in ch department of microbiology
GLOVER, W J, M.B Belf, F.F A R.C.S., D OBST consultant anæs

Nottingham Health Services

BOSTOCK, A D, M.B Manc., D P H senior M.O
FRASER, I G P M B Edin., D P.H senior M.O
MATHESON, K. W, M B Edin, D C.H, D P.H deputy M.O.H
PALMER W L., M.B Durh, D T M. & H, D.P H senior assistant M O
PLOWRIGHT, NELLIE M, M B Birm, D.C.H, D P.H senior assistant M.O
STOREY, DORIS, M.B Durh, D.P.H senior assistant M.O

Notes and News

THE CONGO

HE primary objective of the emergency period on the th side of the United-Nations operation in the Congo[1] [2] has n achieved, according to Dr J S McKenzie Pollock, H O senior representative. There are now in the country ugh medical personnel, consisting of Red Cross and vernment teams, to staff all provincial and the main district pitals, even if the hundred or so remaining Belgian doctors e to leave There are 25 medical teams from 23 countries, rdinated by W H O

7 H.O gives news of the following teams besides those named week[2] two Canadian Red Cross, a second Australian Red Cross, akistani Red Cross, an Iranian team, and a Swiss medical unit. n addition there are 28 W H O personnel, including the member W.H O advisory team to the Central Ministry of alth. This team has completed a preliminary survey of the ieral health services of the country, and has made recommendations for a suggested permanent establishment in the ngo To staff a basic health service, as recommended by the visory team, about 650 medical personnel would be required the following categories doctors, pharmacists, dentists, rses, midwives, sanitarians, biologists, sanitary engineers, d technicians This number does not include provision for training programme which will be needed over a long riod gradually to qualify Congolese to fill the posts which, the time being, will have to be staffed from outside A tailed programme for such training of Congolese staff is ing prepared by the W.H O advisory team, in consultation ith the Ministry of Health. The province of Katanga is not cluded because its final personnel requirements are still iknown.

The second objective of the emergency period—to reactivate ie public-health services of the country—has been only partly hieved, according to the W H O report. Water-supplies i the large towns are being controlled and maintained with ie help of W H O and public-health engineers from Government teams Short training courses have been organised for ie Congolese maintenance staff of water-supply installations 'ector-control services and routine sanitation services have een restarted in most provincial centres It has not yet been ossible to reactivate the epidemic control services in rural istricts, because of lack of supervisory personnel

In Kasai province, a smallpox outbreak has been investigated nd is considered to be a continuation of the local endemic ituation. A smallpox outbreak in the Banningville area is eing investigated A plague outbreak reported from the Lac lbert area is being investigated by the health team at Bunia. lissionary and voluntary-agency medical services are proving heir worth in the emergency, and, in many instances, nissionary doctors are helping to maintain basic services at Government installations

THE BEITS AND THEIR FELLOWSHIP

To perpetuate a name, the endowment of learning is at least as effective as memorial masonry The Graham chair of pathology and the William Julius Mickle fellowship are as likely to survive as the Nelson column. But who were Graham and Mickle and why do we owe these endowments to their bounty? Because few can answer such questions without reference to the *D.N B*, the trustees of the Beit Memorial Fellowships have done well to celebrate the fiftieth anniversary of this foundation with a booklet which tells its history[3]

In the first years of this century a plan was hatched to transfer the preclinical teaching of the medical sciences in London from the hospitals to two or three large institutes For this purpose Alfred Beit, a former associate of Cecil Rhodes, subscribed £25,000 and promised a legacy of the same size. When, for better or worse, the scheme foundered on the opposition of the preclinical teachers, and the contributions were returned to the donors, Dr James Kingston Fowler (in cooperation with Prof E H Starling and Dr John Rose Bradford) drafted a plan for using these funds to found three research fellowships in medicine. On Alfred Beit's death in 1906, his contribution and the rest of his large fortune went to his brother Otto (born in Hamburg in 1865) who had prospered in business in the City of London Otto Beit took an active personal interest in Dr Fowler's new proposals and eventually gave not only the £50,000 but enough to endow the fellowships, in his brother's memory, with £215,000

It is because of these early connections that the Principal of London University was (and is) one of the trustees The others were the founder until his death in 1930, Sir James Kingston Fowler, and three distinguished public figures The trustees are advised by a small board made up of men of eminence in medicine and science, one of whom acts as secretary The secretaries have been Dr Fowler, Prof T R. Elliott, Sir Alan Drury, Prof A. A. Miles, and now Sir Roy Cameron

The first awards were made in 1909 In 1922 senior fellowships were added. From time to time the value of all fellowships has been increased. Until 1945 the fellows had to be of European descent, but the awards have since been open to any graduate of a university within the Commonwealth and the restriction to medical graduates has been removed. No money is ever given for bricks and mortar or for the expenses of research.

When the Beit fellowships were founded, the openings for the young man who wished to do research were few and restricted The names of the early fellows and their subsequent careers (e g., Thomas Lewis, T R. Elliott, and Edward Mellanby) demonstrate that they filled a need. Since then two fellows have gained the Order of Merit, two have been Nobel prizemen, one has been ennobled and eight knighted, and forty-two have been elected to the Royal Society Today the entry to a career in research is no harder than entry to surgery, but a Beit fellowship continues to be a mark of especial distinction *Esto perpetua.*

AMENITY BEDS IN SCOTTISH HOSPITALS

THE Department of Health for Scotland is asking hospitals to review their provision of "amenity" beds and make it more widely known

In the National Health Service patients who need privacy on medical grounds have the first claim to the single rooms or small wards But, when not required for that purpose, beds in these rooms or wards may be given to patients willing to pay a charge This charge varies from hospital to hospital, but it is always between a third and half of the cost of maintaining a patient in that hospital

The Department hopes that hospitals will do what they can to provide amenity beds wherever the demand justifies it, but makes it clear to the public that willingness to pay for such a bed will not secure earlier admission to hospital "as in the past, hospital admissions will be determined by medical priorities" The amenity bed is for National Health Service patients and not for the private patients of consultants

PANORAMIC DENTAL RADIOGRAPHY

NOW that more is known of the cumulative effect of radiation, greater attention is being given to the need for reducing exposure during radiographic examinations Faster films and better-screened X-ray apparatus are available, and the application of television techniques has yielded the electronic image-intensifier[1] Dental radiography makes only a small contribution to the total amount of man-made radiation to which a patient may be subjected, but it is one that could be reduced still further

The usual dental X-ray machine operates at about 55–60 kV and the tube current is 10 milliamps (or 5 milliamps for some of the

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1. See *Lancet* Aug 13, 1960, p 358.
2. *ibid.* Sept. 3 1960, p 555
3. The Beit Memorial Fellowships for Medical Research 1909–1959 Privately printed by the trustees. 1960

1 *Electronic Engng*, 1959, 31, 352

smaller sets), the exposure-time for a single film may be anything up to 1 second, although good periapical radiographs may be taken in 0 3–0 5 second on some of the faster films As the American Academy of Oral Roentgenology points out, many dental surgeons over-expose and under-develop their films A full-mouth examination usually requires seven films, and may need fourteen, and accordingly many workers consider that routine radiographic surveys —however valuable—of children's teeth are hardly justifiable, or even practicable

Dr S Blackman, director of the department of radiology of the Royal Dental Hospital, has kindly given us details of a new Swiss X-ray tube—the 'Panoramix'—with which a view of the whole dentition may be taken on one film in 0 3 second.

This tube resembles the "insertion anode" type which has been in use in industry for some years The focal spot is only 0 004 in in diameter and the anode, which is at the end of a tubular glass extension of the X-ray bulb, can be placed in the mouth The anode emits a wide-angle divergent beam which gives an undistorted panoramic view of all the teeth and their supporting structures on a 10×4 in film held against the outside of the face

Measurements made on a prototype tube showed that, for an exposure of 0 15 milliamp-second at 56 kV the dose is about 2 5 roentgen at 1 5 cm from the anode, falling to 1 5 roentgen at 5 cm, without additional filtration The tongue, because of its nearness to the anode, would receive between 3 and 5 roentgens , Shields are being designed to reduce this dose, and also that to the brain, the spine, and lymphatic tissue Dr Blackman expects that the gonadal dose—already small in conventional dental radiography—will be too low to be measured by normal methods

This tube is to form part of a mobile unit which is now under development, and a pilot survey to assess the possibilities of mass dental radiography for schoolchildren is planned for October

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University of London

The following degrees have been awarded

M D—C J Wardle, M L N Willoughby
M S—Owen Daniel, A. J Harrold

Royal College of Physicians of London

Sir Francis Fraser will deliver the Harveian oration on Tuesday, Oct 18, at 3 P M, at the college, Pall Mall East, S W 1 His subject will be the Challenge to the Medical Profession

Association for the Study of Medical Education

This Association will hold a symposium at the Royal College of Physicians of London, Pall Mall East, S W 1, on Friday, Dec 2, on the functions and structure of the teaching hospital

Scholarships to Winchester College

Wilson-Barkworth Fund—Grants from this fund are available to help in the education at Winchester College of sons of members of the Royal College of Surgeons of England Further particulars may be had from the clerk to the trustees of the Fund, Messrs Gray Bodsworth & Cobb, Duncombe Place, York

Medical Research Council Fellowships

Applications are invited for the following travelling fellowships and scholarships available through the Council for 1961–62

(1) Rockefeller travelling fellowships, (2) Sir Henry Wellcome travelling fellowships, (3) United States Public Health Service fellowships, (4) Lilly foreign fellowships, (5) Lederle travelling fellowships, (6) Dorothy Temple Cross research fellowships in tuberculosis, (7) Alexander Pigott Wernher travelling fellowships in ophthalmology and otology, (8) French exchange scholarships in medical science Further information and application forms may be had from the secretary of the Council, 38, Old Queen Street, Westminster, S W 1, and the closing date for applications is Oct. 31

International Cancer Congress

This congress will be held in Moscow from July 23 to 28, 1962 Particulars may be had from the general secretary of the congress, Prof L Shabad, Academy of Medical Sciences of the U S S R., 11, Solyanka, Moscow, U S S R

World Health Organisation

Dr Fred Grundy, Mansel Talbot professor of preve medicine in the Welsh National School of Medicine, C has been appointed an assistant director-general of W The position of fourth assistant director-general has lately created, and as its first holder Dr Grundy will be respo for the divisions of public-health services, of health prot and promotion, and of education and training He is exp to take up his duties at the beginning of 1961

Dr Grundy was born in 1905 in Bradford, Yorkshire, and gr ated M B in the University of Leeds in 1927 After one y hospital work he entered the public-health service and held ap ments in Suffolk and Willesden, eventually becoming medical of health of Luton He was called to the bar in 1931 Amo publications are two textbooks of preventive and social m and he was a co-author of a study on undergraduate and postgr education in nineteen countries, which appeared in the W monograph series He also has acted as a W H O consultant Expert Committee on Postgraduate Training in the Public H Aspects of Nuclear Energy, and he has visited Ceylon to advis Government on public-health law

Occupational Health

A course on this subject will be held for general practitio and industrial medical officers from Monday, Sept. 2 Saturday, Oct 1, at the London School of Hygiene and Trop Medicine, Keppel Street, W C 1 Further particulars may found in our advertisement columns

International Congress of Neuropathology

This congress will be held in Munich from Sept 4 to 8, 1 Further particulars may be had from the general secretar the congress, Prof H Jacob, Universitätsnervenklinik, O bergstrasse 8, Marburg/Lahn, Germany Intending tributors from Great Britain should forward titles without d to Prof C E Lumsden, School of Medicine, Leeds, 1

Sir Gordon Covell has been awarded the Walter Reed med the American Academy of Science in recognition of his contrib to tropical medicine

Lord Twining will give the inaugural address at King's C Hospital Medical School, Denmark Hill, London, S E 5, on Fr Sept 30, at 3 P M

Particulars of a refresher course in ophthalmology to be h the Courage Laboratory of the Royal Eye Hospital, St Geo Circus, London, S E 1, may be had from Prof Arnold Sors the Courage Laboratory

On Friday, Sept 16, at 5 30 P M, at the Whitely Wood C University of Sheffield, Dr Karl Menninger, of Topeka, will s on psychiatric case study

Prof R E Lane has been appointed a member of the Governm research study group on toxic chemicals used in agriculture and storage, in succession to Dr Donald Hunter who has resigned.

The annual dinner of the Yorkshire Glasgow Graduates Associ will be held on Oct 7 in the Hotel Metropole, Leeds, wh Compton Mackenzie will be the guest of honour Further part may be had from Mr James Wishart, 33, Manor Row, Bradfo

The annual dinner of past and present men students of the L School of Medicine will be held at the Griffin Hotel, Leeds, Friday, Oct 14, at 7 P M Further particulars and tickets (27 may be had from Mr Jeffrey Ellis, at the medical school.

Dr Hugh Garland, Dr Michael Ashby, Dr E R. Bicker Dr Roger Gilliatt, Dr W B Matthews, Dr Henry Mille Dr B G Parsons-Smith are to visit Bucharest and other ce as guests of the Academy of Medical Sciences of the Rum People's Republic from Sept. 10 to 20

CORRIGENDUM *Detection of Epidemic Strains of* Staph aure In table III of the article by Dr B Moore (Aug 27, p 453) one s of phage-type 29 52 52A/79 80 was shown as mercury sensiti fact the single strain of this type examined was mercury res On the last line of the same table the phage type should read 29 52 52A/79 In fig 3 the phage-type shown as 55/77 should 75 77

The Lancet · Saturday 17 September 1960

THE EVOLUTION OF MODERN OBSTETRICS

Sir Dugald Baird
M.D, B Sc., LL D Glasg, F.R.C O G, D P H
REGIUS PROFESSOR OF MIDWIFERY AND GYNÆCOLOGY, UNIVERSITY OF ABERDEEN

(concluded from p 564)

II

What changes have there been in the attitude of women o childbearing, and what effect have these had on the maternity services? I shall here describe the evolution of the maternity services and the adjustments that seem necessary in the training of the medical student, the general-practitioner obstetrician, and the obstetric specialist

The Mother

In 1861–69 the average family contained 6·16 children, by 1900–09 the number had fallen to 3 30, and in 1934–37 t was 2 04, the lowest on record This coincided with a very low marriage-rate and the appointment of a Royal Commission on Population, which sat during most of the war years Its excellent report aroused little general interest, since publication coincided with a post-war rise in the birth and marriage rates

Marriage is now taking place earlier for example, in 1957 55% of women in the age-group 20–24 were married, compared to 32% in 1938 Formerly, early marriages were associated with large families, but this is no longer so It is estimated that when the women who married in 1952 have completed their childbearing the average family size will be 2 21 (Registrar General 1957) The fact that the average family size remains small despite the rising standard of living and early marriage makes it clear that most women now have children because they want them and not because they cannot prevent pregnancy The improved health and growth of young mothers should help to ensure that reproductive wastage is kept to a minimum

The attitude of women to the discomforts of labour seems more balanced than it was They recognise that labour is less of a trial if they adopt a calm and confident approach to childbirth encouraged by sympathetic doctors and midwives But at the same time they expect as much relief as possible from unnecessary suffering Obstetricians and anæsthetists have responded by devising better methods of relieving pain, and there is no doubt that the standard of anæsthesia and analgesia has improved remarkably in the last ten years

But the change in reproductive habits brings its own problems when plans go wrong Parents in all social classes are much more ambitious for their children than formerly, as is indicated by the much larger numbers coming forward for secondary and university education and the much bigger proportion coming from "working-class" homes When an unwanted pregnancy occurs, the emotional upset is often greatest in those who are most ambitious for their children Such women need a great deal of help, and occasionally a heaping-up of circumstances may drive a woman to breaking-point, so that termination of the pregnancy may be necessary Again, there are still many women who are worn out by repeated pregnancies Often of poor physique initially, especially those living in the slums of our large cities, they seem incapable of avoiding pregnancy Although maternal mortality is relatively high amongst them, they are characteristically much less disturbed emotionally by an unwanted pregnancy than women with more education and higher ambitions Since contraceptive advice is more or less useless in such cases, sterilisation should be used much more frequently, and in my experience it is welcomed Used with discretion, postpartum sterilisation can greatly improve the physical and mental health of the mother and the general wellbeing of the family circle, and is therefore good preventive medicine

The Services

Just after the first world war most confinements took place in the home Since the 1911 National Health Insurance Act did not provide for the medical care of mother and child, a doctor was not freely available and many women could not afford a medical fee To fill the gap, the Government, through the local authorities, set up antenatal clinics, and by 1935 there were about 1400 State-aided clinics in England and Wales In some voluntary hospitals, part or all of the cost of treatment of both antenatal outpatients and inpatients was borne by the local authorities This service has helped to raise the standard of antenatal and child care to its present high level Now that every mother has a family doctor, the future of the maternity and child-welfare service is in doubt, but any attempt to dispense with it at present would be dangerous, since most practitioners have neither the time nor the facilities for health education The great pressure on his time would force the practitioner to neglect the educational and preventive aspects of his work because of the more pressing need to treat illness and disease One hopes that this may be remedied and that in the future the family doctor will play a bigger part in preventive medicine

In the 1920s the training of the family doctor in midwifery was very unsatisfactory and he had to learn from experience under most unfavourable conditions Some measure of the low standard of obstetrics was the frequency of what was known as the "failed forceps outside" type of case In the years 1925–34, 426 cases were admitted to the Glasgow Maternity Hospital after an unsuccessful attempt by the general practitioner to deliver with forceps in the patient's home The maternal mortality was 14% During the years 1932–34, 167 "failed forceps" cases were sent in by 121 practitioners 95 doctors sent one case each, but 3 doctors were together responsible for twenty cases, and one of them sent in a total of 9 cases in the three years This doctor had acquired the reputation, in the poorer parts of the city, of being able to deliver the baby with the minimum delay when sent for by the tired midwife

It must be pointed out, however, that failure to deliver the baby with forceps occurred inside the hospital as well as outside, sometimes even in booked cases During 1925–34, 373 craniotomies were performed with a maternal mortality of 9% These deplorable figures may to some extent be excused if it is remembered that cæsarean section in such cases carried an even higher death-rate

Maternity Hospitals

In the inter-war years our maternity hospitals were seriously defective Their size and number were determined not by the needs of the community but by the money available In sharp contrast to children's hospitals, maternity hospitals have always found it difficult to attract donations of money from the public, perhaps because many were founded originally primarily to care for unmarried and destitute mothers Thus, many of our leading maternity hospitals were, and still are, overcrowded, ill equipped, and in some respects dangerous places Antenatal clinics attached to the hospitals are often equally defective When they were planned there was no appointments system and little waiting accommodation, it was a common sight to see expectant mothers queuing in the street for an hour before the doors opened

The obstetricians attached to such hospitals comprised all the leading teachers in the country, but their professional outlook was, with a few exceptions, restricted to the technical details of operations and the internal affairs of the hospital The wider problem of the needs of the area and of the services required to meet them was not their responsibility The effect of this restriction of outlook can still be seen in the form and content of the annual medical reports which are compiled by most leading maternity hospitals These reports contain little more than a list of abnormal cases treated and the outcome for the mother and child The results of treatment vary greatly with the type of patients treated, the kind of community in which the hospital is situated, and whether the cases are booked or emergency, and on the proportion of each Consequently, conclusions regarding the effect of treatment are difficult to draw and comparison of the results from different hospitals are often very misleading Even comparisons of the results in the same hospital over a period of years may be misleading because of general factors whose influence cannot be measured What is wanted is an analysis, on sound epidemiological lines, of all the births in a region

There has been a steady drift towards hospital confinement In England and Wales in 1925, 15% of live births took place in hospital, by 1937 it had reached 40% and by 1957 65% In Scotland, since 1948, the teaching hospitals have been an integral part of the regional hospital service This has allowed planning of a regional maternity service, with the teaching hospital as the central point of the service in each area The importance of having the university departments of child health, preventive medicine, and obstetrics linked closely to the hospitals and to the public health service cannot be overstated It has been argued that the staff of the teaching hospital will dissipate its time and energy by such a process, but I am sure that the danger can be avoided by adequate staffing and proper delegation of duties The advantages to the universities are very great because clinical teachers have an opportunity to gain a wide perspective At the same time, the universities have the duty as well as the opportunity of acting as leaders in advancing the standard of medical care They can work in close association with consultants and other members of the obstetrical staff of the hospital, so that the organisation of the maternity services, methods of treatment of patients, and training of undergraduates and postgraduates can be planned and integrated

The fact that the stillbirth-rate in the City of Aberdeen in 1957 is little more than a third of the rate in 1937 is partly due to the fact that the staff of the university department is closely integrated with the Natio Health Service staff, and is able to supply the stimul necessary to maintain a high standard of care, to condu research, and to test scientifically any new method treatment suggested by research Another factor is th increase in the incidence of hospital delivery from to over 80% during the period Since all the matern beds in the city are in the teaching hospital, the proble of ensuring a uniformly high standard of obstetric ca is simplified Another very favourable factor in Aberdee has been the great help and cooperation given by th medical officer of health and his staff of midwives, heal visitors, and maternity and child-welfare officers As result the educational and preventive aspects of midwife have been thoroughly taught, and overlapping of effo has been avoided Detailed statistical analysis of births in the city, irrespective of the place of confinemen is made annually An accurate picture of progress therefore available, and the measures necessary for furth progress can be discussed on the basis of numerical fa Whatever modifications may be introduced in the futur there is no doubt that the present method of organisatio has reduced the perinatal mortality more quickly tha would have been possible in any other way

The organisation of a maternity service is peculiar difficult for two reasons Firstly, it is impossible to te when labour will start, so that a fully staffed servic irrespective of the load of cases, must be maintained nig and day, and secondly, the onset of many serious com plications of pregnancy and labour is unexpected an sudden, so that special facilities must be constantl available at short notice Hence only a large maternit hospital can be fully competent to deal fairly economicall with all eventualities

A local maternity service in towns and cities shoul therefore be built round a centrally placed matern hospital which should take all primigravida, all poten tially abnormal multipara, and all those who requi hospital confinement for social reasons Very large citie should be divided into sectors with a maternity hospit at the centre of each In Aberdeen we are fortuna enough to be able to admit not only those women fo whom hospital confinement is desirable but also those wh prefer to be confined in hospital We can therefore avoi distasteful selection of cases and the unhappiness cause by it Some women prefer to have their babies at hom for them the domiciliary service of general-practitione obstetricians and midwives is available, but the hospit service must be able to give effective help when a emergency arises

While there is much to be said for making a larg maternity hospital the central point of the materni service, it is not a good plan to concentrate all antenat and postnatal clinics in the centre The normal patie should attend a clinic in her own area which works i close association with the child-welfare clinic In this wa the patient comes under the influence of the child-welfar department Health education can be given both at th clinic and in the patient's home An obstetrician fro the central hospital can attend at regular intervals to tak part in the antenatal care It may be possible to arrang that selected general practitioners take a large amount of the work at such clinics Abnormal cases are best seen at an outpatient clinic at the hospital centre, where special investigations can readily be made and a consultant's opinion obtained

In domiciliary midwifery in the poorer parts of larg ities general practitioners and midwives have to contend with poor facilities and with lack of intelligent cooperation from many of their patients Many doctors work in isolation and are not accustomed to discuss their problems with colleagues This is in marked contrast to the state of affairs in hospital, where more and more the emphasis is on team-work, with free discussion of methods of [illegible] and constant appraisal of the results of treatment Domiciliary confinement is no doubt psychologically helpful to many mothers, but the advantage from the point of view of safety is certainly with the well-equipped and well-run hospital Good running of a hospital naturally includes treating the patient as an individual and with kindness as well as at a high level of technical efficiency

Many general practitioners are now in favour of hospital delivery and a demand for general-practitioner beds in hospitals is growing In country districts, because of the distances involved, the general practitioner must take a great measure of responsibility for the work in the local maternity hospitals But he should be helped by the visiting specialist, who is ultimately responsible to the regional hospital board for the standard of work in these small units In the cities, general-practitioner beds may be attached to the teaching or base hospital as the case may be, and again the practitioner should work in close contact with the specialist team and take part in staff discussions, especially if one of his own cases should come under review It is unrealistic to insist that the consultant should be called in only when requested by the general practitioner, the consultant should be free to keep in touch with practitioners on his own initiative, and to give informal advice when he feels it is necessary

While much of antenatal care is within the competence of any conscientious family doctor, operative obstetrics cannot be taught to all medical students For operations such as surgical induction, delivery by forceps, or the repair of vaginal lacerations the doctor must acquire his skill after graduation, as a resident house-surgeon in a maternity hospital, and this skill must thereafter be maintained by regular practice A general practitioner cannot have regular and sufficient experience of obstetrics unless he is attached to, or becomes a member of, a fairly big group practice where each member of the group has a special interest and acts as the link between his colleagues and the specialist in that particular branch of medicine—in this case, the obstetrician and gynæcologist

Administratively, the maternity services in Britain are untidy, the Guillebaud Committee went so far as to say that they are in a state of confusion But the Cranbrook Committee in England and the Montgomery Committee in Scotland thought that the tripartite structure of the maternity services should be retained, because it would not be practicable to transfer the maternity services alone to hospital control when all other health services remain tripartite The Cranbrook Committee proposed that local maternity liaison committees with a professional membership should be formed to ensure that local provision for maternity care is utilised to the best advantage Local clinical meetings should be encouraged so that all persons in an area responsible for carrying out maternity care can discuss the clinical aspects of maternity cases The Montgomery Committee thought that area professional advisory committees might be set up to make recommendations as to how the service could be coordinated and improved at the professional level

Both committees thought that a minimum of 70% of hospital confinement would be a reasonable aim in Britain There are great differences throughout the world in the incidence of hospital confinements In many of the highly developed countries, particularly in the U S A and Scandinavia, the proportion of women delivered in hospital is very high—e g , 96% in Sweden In Holland, on the other hand, hospital delivery is only about 30% The stillbirth-rate is very little higher in Holland than in Sweden, and both are low by British standards The Dutch example shows that given a very well-organised maternity service and a very high standard of physique and health of expectant mothers, and certain other favourable environmental and social conditions, it is possible to have a safe and efficient domiciliary service

In some of the less industrialised regions of England, the perinatal mortality is reasonably low though only about half the deliveries take place in hospital In the heavily industrialised areas, on the other hand, it is generally high, irrespective of the proportion of hospital deliveries For example, in Wales in 1957 it was 44 per 1000, despite a hospital-delivery rate of 67% In such areas, the home conditions are often unsuitable for delivery because of overcrowding, poor water-supply, and lack of other amenities, in addition, because the health and physique of mothers tends to be poor, complications of pregnancy and labour are frequent and serious

The mere fact that delivery takes place in hospital does not ensure that all will be well, but it does lessen the risk It is particularly important to have enough beds for antenatal complications and the number required increases as the level of health of the community declines In Aberdeen, we have calculated that 8 antenatal beds per 1000 deliveries are required, and about a third of all cases booked for confinement are admitted for treatment at some stage of pregnancy Many women in the city, especially multiparæ in the lower social classes, would benefit greatly in health if they were relieved of some household duties towards the end of pregnancy Their improvement during a short stay in hospital is often quite striking, but some simpler form of accommodation in a hostel or convalescent home would be sufficient If there is an overall shortage of beds, it may be better, as suggested by Theobald (1959), to discharge suitable patients to their homes early in the puerperium, rather than reduce the beds available for antenatal cases

Medical Education

Undergraduates

Only a proportion of doctors will practise obstetrics and only those who have had postgraduate experience should do operative obstetrics We should therefore concentrate on giving students a broad view of the problems of human reproduction and spend less time on the management of abnormalities in labour

The student should have a clear understanding of the physiological changes of pregnancy—the influence of heredity and environment on reproduction, the influence of age, emotional factors, and customs on reproduction and on sex function in general The problems of health education, preparation for marriage, and family planning should also be considered He should, of course, understand the mechanism of labour and the various abnormalities which occur, but it is not possible to give him enough practical experience to become skilful in the procedures which sometimes become necessary even when uncomplicated delivery has been expected The purpose of undergraduate training, in short, should be to turn out a man who knows the "natural history" of human reproduction and who can take a comprehensive view of the general as well as the medical problems of having a family He should not, however, be led to consider himself fully equipped, without postgraduate training, to undertake obstetric practice

Postgraduates

General-practitioner obstetrician—The family doctor who wishes to take full responsibility for his patient during labour as well as during the pregnancy should hold a resident post in a maternity hospital for six months, after which he should be competent to repair a torn perineum, deliver with forceps, and remove a placenta manually He should then be encouraged to take the diploma in obstetrics of the Royal College of Obstetricians and Gynæcologists This type of training should lead to a high standard of obstetrics amongst general practioners, especially if general practice is organised so that the well-trained practitioner can remain up to date and efficient

Obstetric specialist—Twenty-five years ago there were few paid training posts even in the leading teaching hospitals, and no recognised system of instruction of specialists existed Consequently the standard of clinical practice varied greatly The Royal College of Obstetricians and Gynæcologists, since its foundation in 1929, has done much to improve the training of specialists, not only by holding examinations but by laying down standards of practical training As a result the standards of obstetric practice have been raised throughout the country as a whole to a high level

Till the advent of the National Health Service almost the only goal for the young obstetrician was a busy private practice, yielding a good income and an interesting and varied professional life in which teaching often accompanied clinical work But the obstetric specialist, especially if he is attached to a teaching centre, can no longer afford to concern himself solely with hospital routines and with building up a private practice He should also be responsible for advising on regional needs, for raising standards of treatment by non-specialists, for relating the teaching of obstetrics to modern requirements, and for fostering research The increasing store set by the community on health demands a high degree of technical skill from the specialist, and amid changing conditions he also needs breadth of outlook, foresight, and adaptability He who wishes to lead in his field cannot afford to neglect science and the inculcation of the scientific spirit of inquiry We are still familiar with the specialist who emphasises that he is a clinician not a scientist, suggesting that the two ways of life are mutually exclusive In the conditions of private practice research has been almost impossible owing to lack of time and facilities, and even in hospital the specialist's time is fully occupied with the care of many seriously ill patients who require urgent treatment

Those consultants who have been brought up under the old system lay stress on the value of private practice as a training, since it allows the consultant to take more interest in the patient as an individual, brings him more into contact with the family doctor and the patient's home, and thus gives him more insight and understanding In hospital, because much of the treatment is given by house-surgeons and registrars, he may have little opportunity to talk to the patient alone There is a tendency for the patient to become a case, and the importance of considering her illness in relation to her home background may be overlooked Hospital treatment c not be impersonal, but with a relatively small staff, a large number of patients to be treated, it is not eas organise work so that continuity of treatment by person is assured Nevertheless an atmosphere which acceptable to patients can be inculcated if medical nursing staffs work as a team, if consultants set an exam of sympathetic understanding of the patient, and if c records are so detailed that even a "new" doctor c approach a patient knowing a good deal about her a person Under such conditions the patient devel confidence in the staff of a hospital rather than in individual doctor or midwife

Medicine is advancing so rapidly, methods of inve gation are becoming so complex, and the standard treatment is becoming so high that the system wh served well in the past will not suffice in the future T great need today is to maintain contact with the vari other branches of medicine Obstetricians need help some aspects of radical surgery, medical complicat of pregnancy, radiotherapy, the care of the newbo obstetric anæsthesia, genetics, sociology, and psycholo They also need help from the scientific departments physics, biochemistry, and physiology

Research

Under the present system of specialist train research is not essential, and is, indeed, made very diffi because of the need to amass experience, study textbo and sit examinations The examination system tends favour the orthodox, whereas research is essentially adventure, in which imagination, the critical faculty, even heterodoxy are at a premium In this respe research has much in common with the creative The newly fledged M R C O G is likely to be at leat before he is free from an imposed regime, and experi indicates that unless a man is given a taste of resea before this age, it is difficult to get him started

The earlier obstetricians were preoccupied with t problems of difficult labour When labour came to standstill how was one to get the baby delivered? solve this problem, the Chamberlens invented, and long line of successors improved, the obstetric force Numerous manipulations were devised to manœu the fœtus into the most favourable position for deliv and instruments such as perforators and cranioclasts w invented to destroy it when necessary in the interes the mother The problem of difficult labour, t together with the operative nature of most gynæcolog treatment, explains why the outlook of the obstetr and gynæcologist has long been dominated by surgery why it has usually been considered necessary to take F R C S as well as the M R C O G With better diagnosis good cooperation from surgical colleagues it is less essent in the large teaching centres at least, for the obstetr and gynæcologist to be an expert general surgeon

The main problems today are medical and physiolog rather than surgical The origins of pre-eclampsia eclampsia—the main causes of maternal mortality— as mysterious as those of puerperal sepsis half a cent ago To uncover them, the obstetrician needs a knowledge of the hypertensive and renal diseases, and the factors which alter water and electrolyte metabol Prematurity has replaced birth trauma as the main ca of perinatal mortality, and, although the management the liveborn premature has improved, we know l about the reasons why fœtal growth is impaired or labour starts, whether it be at term or very much earlier The pathologist is often unable to determine the causes of stillbirth and neonatal death Even if the necropsy shows that the immediate "cause" was asphyxia, atelectasis, or immaturity, it cannot show *why* the baby was asphyxiated or was born immature Few standard [illegible] of obstetrics or physiology have much to say about human reproduction after they have dealt with fertilisation and the endocrine changes of early pregnancy, yet there are many clinical phenomena which demand study by physiological methods

For example, the average mother puts on twice as much weight during pregnancy as can be accounted for by the fœtus, placenta, and liquor amnii What is the nature, explanation, and purpose of this disproportionate gain? What happens if the mother gains much more or much less than the average amount? Does the wellbeing of the fœtus depend mainly on the nature and quality of the diet taken by a pregnant woman or can it ensure its own survival by growing when necessary at the expense of the maternal tissues?

Psychology and sociology are also growing in importance in relation to obstetrics Reference has already been made to some of the problems of family planning in modern society Much has been written in recent years about "natural childbirth" It is claimed that the confident, relaxed mother will have an easy and painless delivery compared with that of a worried, tense mother Is this true, or merely an exaggeration of the axiom that the kindly obstetrician will gain the patient's confidence, so that she can face the ordeal of labour in a cheerful frame of mind, caring more about the happy outcome than the present pain?

Few practising clinicians can hope to become masters of the more specialised skills needed for intensive study of biological and sociomedical problems But this does not mean that research is beyond the capacity of the clinician Indeed, the clinician is better qualified than anyone else to undertake the systematic study of ordinary clinical records The value of such study is unquestionable By it, he can assess results, discover trends, and improve treatment By appealing to numerical fact instead of to subjective impressions, he can sharpen clinical judgment and improve the standard of observation in the wards and operating-theatres

As in all other fields of investigation, clinical study on these lines should be properly organised and should make use of reliable and efficient techniques In too many hospitals the records system is run by an officer whose contacts with clinicians are administrative only, or by a succession of young obstetricians in training As *The Lancet* (1960) noted, "the consultants must set the standard and be prepared to supervise the quality of the case-note taking, and themselves take part in transcribing medical information from the case-notes into the records system" They are more likely to do this willingly and intelligently if they themselves use the records system for the purposes of research

In Aberdeen, we have gradually improved our standard of taking case-notes, and a statistical section forms an essential part of our research team We have compiled accurate statistics relating to all births in the City of Aberdeen since 1948, and our assembly of classified records covering the whole of a defined population is probably unique in its scope, flexibility, and accuracy Any reputation we have gained as a centre of epidemiological research is based primarily on the painstaking collection and organisation of thousands of facts by an interested team of senior obstetricians, aided by the staff of the records office of the hospital and the statistical section of the Obstetric Medicine Research Unit

But the study of routine clinical records is clearly insufficient in itself, and a university department has an obligation to apply laboratory and other techniques to the study of obstetric phenomena

We may agree that obstetricians should themselves participate as far as possible in studies involving specialised methods, but they can rarely hope to compete effectively with professionals in the various fields Very few obstetricians have the aptitude and the opportunity—let alone the courage—to step aside from their specialty for a few years in order to be thoroughly trained in a basic science, such as biochemistry For effective research involving biochemistry, obstetricians should therefore seek help from professional biochemists, and similarly with other fields

In Aberdeen, over the past fifteen years, we have built up a team which at the moment includes 19 graduates engaged entirely or partly on research Of the 19, 7 are obstetricians 5 others are medically qualified but not specialist obstetricians, they include a physiologist and an epidemiologist with special experience in nutrition 7 members of the team are not medically qualified, they include 2 chemists, a statistician, and a group engaged in sociological studies

The formation and direction of a mixed team such as this poses many problems quite apart from those of earning and retaining the confidence and support of bodies willing to finance research If they are to be effective, non-medical graduates working in a clinical department must be given a great deal of independence and a status equal to that of their clinical colleagues It is very easy for a scientist in a clinical team to feel an outsider, both professionally and socially Indeed he *is* an outsider in the sense that he has probably stepped off the usual ladder to promotion and advancement in his own specialty If he is not sufficiently experienced to direct his own work, he rapidly loses perspective If, on the other hand, he knows what is needed and is given the freedom to pursue the line that seems best to him, his clinical colleagues will need to be receptive to unfamiliar lines of thought and they must also give him the active support and help he requires in extracting information or biological materials from patients Teamwork, which is so necessary for progress under modern conditions, involves more than mere collaboration, and its growth is rarely spontaneous Experts with a diversity of skills and technical languages must be induced to talk and to work together, day by day, so that they will develop bonds of mutual interest and understanding

Reproductive life in the human species is a lengthy process, and for the solution of many problems research over a long period must be undertaken This means that a research team should not be regarded as an ephemeral affair to be supported by a patchwork of financial grants and administrative expedients If they are to concentrate on biological problems, whole-time research-workers should not be continually preoccupied by the problem of making a living and obtaining promotion Thus, it becomes necessary to guarantee careers, with adequate security and remuneration, for research-workers who have won their spurs

During the past decade, the Medical Research Council has greatly eased problems of this nature by its enlightened policy with regard to clinical research, and by forming numerous permanent research units of which the Obstetric Medicine Research Unit in Aberdeen is one The unit is housed partly in the university department of midwifery and partly in special accommodation forming an integral part of the Aberdeen Maternity Hospital and built with funds given to Aberdeen University by the Scottish Hospital Endowments Research Trust With this physical setting, and with a common directorship, the university, hospital, and M R C staffs are able to work very closely together as a team

It will surely be a step in the right direction if more obstetricians are trained in the outlook and methods of research, preferably by working for a period in a team such as this The first need is to adjust the training of the obstetrician to modern requirements by reducing the emphasis on general surgery and by encouraging the growth of medical and physiological skills, preferably in a research setting Beyond that, there is a need to lower the hurdles which make most obstetricians fear for their future if they leave the orthodox path of progression from house-surgeon to consultant I feel sure that the academically minded obstetrician, given an adequate training in research methods, and proper facilities to undertake clinical research, can make important contributions to knowledge, particularly if he is prepared to make research the focus of his career Several physicians have done this, and a few surgeons, but almost no obstetricians Yet I cannot believe that in obstetrics we are willing to leave scientific progress mainly to the efforts of others

Conclusions

Great progress has been made in obstetrics during the past twenty-five years Much of this has followed the application of specific discoveries, but there have also been advances in clinical technique and in the organisation of the maternity services With a rising standard of living, the health, nutrition, and level of hygiene of the population have improved Better-educated parents have taken full advantage of the services provided, and now take steps to plan their families so that they can bring up their children well

These scientific and social changes have been accompanied by a dramatic reduction of maternal mortality, but perinatal mortality, after responding in a striking manner before 1948, has, in England and Wales, been almost stationary during the past decade, at about 36 per 1000 births

We may expect that continued social improvement, with an earlier average age at the birth of the first child, will of itself result in a gradual fall in the perinatal death-rate But there is evidence that a higher standard of obstetrics could quickly lower perinatal mortality in areas where it is now above average Where a rate of 30 or less has been reached, present methods of treatment have probably almost reached their limit of usefulness

To ensure further progress, an ever greater rise in the level of maternal health and physique will be necessary And to deal effectively with the disorders of pregnancy that arise in a generally healthy population the obstetricians of the future will need to know more about the physiology of pregnancy and the meaning of the variations of efficiency associated with age, parity, and physique The significance of factors such as these is ultimately bound up with the social context and environment in which women live Therefore, the leaders in the field of obstetrics must not only be good physiologists, physicians, and surgeons, they must also know some of sociology and psychology, and of vital statistics T widening of the field of obstetrics to cover all aspec human reproduction should attract enough entran the high calibre necessary to ensure further progres this uniquely interesting branch of medicine

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A CHEMICAL AND BACTERIOLOGICAL STUDY OF GALLSTONES

THE PRESENCE OF AN ACTINOMYCETE

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CHEMICAL analysis has been the means of inquiry in the cause of gallstone formation for over a hundred ye (Thomson 1833) By the 1890s knowledge concerning ga bladder disease was sufficient to allow the publicati (1892) of a monograph by Naunyn entitled *A Treatise Cholelithiasis* wherein is expounded a theory—name that many of the stones in which cholesterol and bil pigments are mixed originate from those pultaceo masses of biliary debris which are sometimes found in t diseased gallbladder A crust of cholesterol forms arou each mass and by crystallisation inwards gradual transforms it into a stone (cholesterinisation), th accounting for the soft friable centres of some " mixed stones Other kinds of gallstones have a hard centre, a Naunyn believed that these started as a nucleus of calciu bilirubinate in the same way as pure pigment ston Rovsing (1924) was to postulate that all types of gallston are formed around such a central nucleus of pigmen which in its turn is derived from a minute cast of t hepatic canaliculi, formed as a result of hepatic d function and then carried in the bile to the gallbladder

The primary cause of the chemical changes by wh stones are formed, however, was considered by Naun and his contemporaries to be the result of inflammati of the wall of the gallbladder, a " lithigenous catarrh The new science of bacteriology had opened up the w for investigation in this field (Gallippe 1886) It w found that normal bile is sterile In acute cholecysti organisms such as the coli-typhoid group could b isolated By 1890 Welch (according to Cushing, 18 had isolated *Bacillus coli* (*Escherichia coli*) and th typhoid bacilli from gallstones Richardson (18 observed the " clumping " of the bacilli in the bile typhoid cholecystitis, a phenomenon suggestive of gigantic Widal reaction within the gallbladder

Thus the emphasis of research into gallstone formation as put upon the hypothesis that blood-borne organisms, uch as *E coli* and *Bacillus typhosus*, reached the wall of he gallbladder and then by the exfoliation of inflammaory cells, the production of abnormal protein and their ctual presence in the bile caused the centre of stones to orm Gilbert and Fournier (1897) demonstrated in nimals that stones could be formed after the intravenous njection of attenuated cultures of typhoid bacilli ollowing the same pattern of research Rosenow (1914), Wilkie (1927), and Illingworth (1927) showed that the most commonly found organism in the wall of the gallbladder and cystic gland was the streptococcus or *E coli* nd that stones could be formed experimentally after ntravenous injection of these organisms (Rosenow, Wilkie) Cholecystitis, among many other diseases, ppeared to be due to a bacillæmia caused by some focus of infection in the body and it was popular to blame the eeth, the tonsils, and the paranasal sinuses as well as the olon, the cervix, and the prostate

These experiments mainly concerned the cause of holecystitis rather than the primary cause of gallstones, nd the isolation of organisms from the centre of stones was not pursued with such zeal In 1936, Helstrom, in weden, was investigating renal calculi and found taphylococcus within their matrix In the same country, Martensson (1941) published a very comprehensive reatise on the formation of gallstones and drew attention once more to the organisms to be found in stones By direct smear and culture he isolated what he called a ‘ typical ” bacillus—one with pleomorphic and subtilis-like characteristics Following the usual pattern of experiment by inoculation stones were formed in the gall-bladders of rabbits

Programmes of research often involve repetition of the investigations of others In this department the search for the causal phenomena of gallstones has required such studies Thus we are presenting some results of the chemical analysis and the bacteriological study of the stones, our attention being particularly focused on the stone centre or “ nucleus ” Originally a pilot and macroscopic survey of stones had suggested that Rovsing's theory might be correct

Methods and Results

For the purpose of the chemical and bacteriological study of stones from 57 patients it was decided to bisect each stone, after flaming, in the bacteriology department and to prepare first the microscopical specimens and the cultures from one half before proceeding to analyse the other half chemically Thus the bacteriological techniques and results are mentioned first Methods and results of chemical analysis will then be considered

Bacteriological Techniques and Results

Examination of the 57 specimens of gallstones submitted for bacteriological examination (to G J B and J F D S) has yielded 30 isolations in pure culture of an actinomycete (fig 1) This organism grew only very slowly in primary culture under strict anaerobic conditions, requiring from 10 to 87 days' incubation before it appeared in the preparations made from the original meat-broth cultures By reason of the findings the bacteriological work required is extensive and associated with many complex problems As this is, in some degree, a preliminary report we (G J B and J F D S) shall not here describe all our techniques in detail, but confine ourselves to the two on which our present work has been based

Preparation of microscopical specimens from gallstones —A drop of sterile plasma, which has been filtered through a bacterial filter, is placed on a clean grease-free microscope slide, and small flakes of a gallstone to be examined are placed on it and then ground to a paste with a sterile platinum loop or needle The paste is then spread thinly and evenly on the slide, is air-dried, and is then fixed with methyl-alcohol and stained by Gram's method (fig 2)

Preparation of agglutinating suspensions of actinomyces —A pure culture of the organism is transferred to 3 tubes of glucose broth which are incubated anaerobically at 37°C for seven days The cultures are then centrifuged and 0 5 ml of 0 01 *N* sodium carbonate and a trace of powdered trypsin (enough to cover a knife-point), are added to the pooled deposit from the cultures The mixture is incubated at 37°C for eighteen hours in a sterile tube closed with a rubber bung After this incubation, 1 ml of acid alcohol (5 parts *N* HCl to 95 parts of absolute alcohol), is added to the mixture, which is then allowed to stand for three to five minutes at room-temperature At this stage precipitation of the bacterial protein occurs and is visible as a flaky deposit. This deposit is now centrifuged and washed in several changes of sterile saline (0 85%) by rapidly decanting the supernatant saline and adding fresh saline between successive centrifugings This process results in the production of even suspensions of the organisms which are satisfactory for agglutination tests Our agglutination reactions have been performed at a temperature of 40°C acting for eighteen hours, before the results are read.

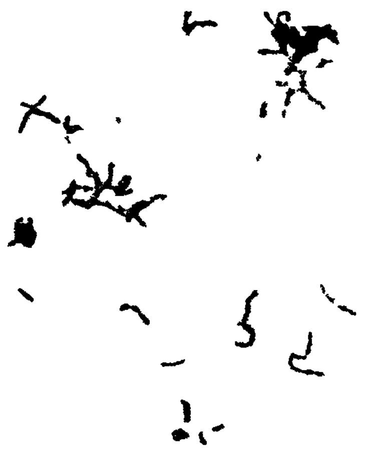

Fig 1—Preparation from anaerobic culture of gallstone showing branching and pleomorphic actinomyces

Serological Character of the Actinomyces

Table I shows that the actinomyces isolated from the stones are homogeneous in their serological characters, when tested against experimental immune rabbit sera, and that they differ distinctly in such serological characters from *Actinomyces bovis* of Wolff and Israel

Chemical Analysis and Expression of Results

After bisection and bacteriological sampling of the stones, drawings were made of each of the 57 specimens to show the appearance of the sectioned surface Details

Fig 2—Preparation of gallstone showing actinomyces. (Gram's stain.)

were recorded of the colouring (table I) and the number of layers (table II). The greater proportion of stones showed either 2 or 3 layers, while 8 stones only were apparently homogenous in constitution. 4 or more distinct layers were found in 6 stones. If clearly defined layering was seen, samples for analysis were carefully taken from each layer, avoiding contamination with material from adjacent layers. If the stone appeared to be homogenous in composition, a small amount was ground to a fine powder for analysis.

The micromethods described by Holt and Tarnoky (1953) were used, tests being performed for the dete of protein, cholesterol, bile-pigments, calcium, phorus, iron, and carbonate. In tables III and I positive results (whether as a “trace”, “positive “strongly positive”) are expressed simply as indic the presence of the substances in the stone. Tab gives the results of analysis of the whole stone table IV the findings in the central layer—or “nucle Homogeneous stones are included in table IV as we table III. The results of culture showing the presen actinomyces are included in each table.

TABLE I—ANALYSIS OF 57 STONES

No in series	Colour and no. of stones	Direct smear	Cultures		Serology (actinomyces)			
			Aerobic bacteria	Actinomyces	Slide agglutination	Tube agglutination	Absorbed sera* cult. 4 (hom.)	Ab
1	Brown, dark yellow, white (1)	–	*E coli*	Absent				
2	Yellow (389)	–	Absent	Present (19 days)	+	1 in 25	–	
3	Yellow, white, green (2)	–	Absent	Present (16 days)	+	1 in 50	–	
4	Grey brown (3)	–	*E coli*	Present (16 days)	+	1 in 25	–	
5	Dark grey and yellow (15)	–	Sterile	Sterile				
6	Grey (1)	–	Absent	Present (17 days)	+	1 in 25	–	
7	Dark brown and grey (40)	–	Absent	Present (17 days)	+	1 in 25	–	
8	Brown (21)	–	*B neapolitanum*	Present (18 days)	+	1 in 50	–	
9	White, grey, brown (1)	–	Absent	Present (14 days)	+	1 in 50	–	
10	Light brown (14)	–	Absent	Present (12 days)	+	1 in 50	–	
11	Grey-white (7)	Gram-+ve rods showing branching. Tight clusters	*Staph albus*	Present (12 days)	+	1 in 50	–	
12	White, grey, brown (1)	–	Absent	Present (10 days)	+	1 in 25	–	
13	Yellow (81)	–	Sterile	Sterile				
14	Cream, rust (25)	–	Sterile	Sterile				
15	Black (1)	–	Sterile	Sterile				
16	Pale cream (4)	–	Gram-+ve rods slender and slightly beaded, showing very scanty branching. Grows aerobically and anaerobically. Colony, moist flat entire edge ? corynebacterium					
17	Deep red (1)	–	*E coli*	Absent				
18	Black. Gravel	–	*B acidi lactici*	Absent				
19	Pale yellow. Gravel	–	*B acidi lactici*	Present (19 days)	+	1 in 50	–	
20	Grey (8)	–	Sterile	Sterile				
21	Rust (3)	–	Sterile	Sterile				
22	Pale brown (1)	–	Sterile	Sterile				
23	Dark red (2)	–	*Staph pyogenes*	Absent				
24	Buff (6)	–	Sterile	Sterile				
25	Pale green and off-white (2)	–	Absent	Present (32 days)	+	1 in 50	–	
26	Dark green (2)	–	Contaminated Gram-+ve sporing *B subtilis* type					
27	Cream and green (1)	–	*Staph pyogenes*	Present (16 days)	–	1 in 25	–	
28	Black (2)	Doubtful gram-+ve rods or cocci. Beaded. Very scanty	*Staph albus*	Present (14 days)	+	1 in 50	–	
29	Pale brown (1)	Very scanty gram-+ve rods	*Staph. albus*	Absent				
30	Yellowish cream (1)	–	Sterile	Sterile				
31	Deep yellow (139)	–	Absent	Present (27 days)	+	1 in 50	–	
32	Deep brown (17)	–	Sterile	Sterile				
33	Pale brown (2)	–	Absent	Present (22 days)	+	1 in 50	–	
34	Dark grey (15)	–	Absent	Present (27 days)	+	1 in 125	–	
35	Brown (2)	–	Sterile	Sterile				
36	Off-white (7)	–	Contaminated with spore-forming rod of the subtilis type					
37	Reddish brown (25)	–	*Staph albus*	Absent				–
38	Buff (9)	Very scanty gram-+ve cocco-bacilli	Absent	Present (87 days)	–	1 in 50	–	
39	Cream (1053)	–	Contaminated with spore-forming bacillus					
40	Light brown and black (216)	–	*Staph albus*	Absent				
41	Grey (11)	–	*Staph albus*	Absent				
42	Brown (1)		Sterile	Sterile				–
43	Pale cream (1)	–	Absent	Present (27 days)	+	1 in 50	–	–
44	Pale brown (2)	–	*B coscoroba* (*E coli* immobile)	Present (27 days)	+	1 in 50	–	
45	Dark grey (1)	–	Sterile	Sterile				–
46	Light brown and black (1227)	–	Absent	Present (46 days)	+	1 in 50	–	–
47	Dark grey (5)	–	Absent	Present (57 days)	+	1 in 25	–	–
48	Brown (2)	–	*Aerobacter aerogenes, B neapolitanum, Streptococcus fæcalis*	Present (25 days)	+	1 in 25	–	
49	Dark grey (4)	–	Sterile	Sterile				–
50	Black (1)	–	Absent	Present (12 days)	–	1 in 50	–	
51	Black (1)	–	Contaminated spore-forming bacillus *B subtilis type*					–
52	Pale blue (2)	–	Absent	Present (43 days)	+	1 in 50	–	–
53	Black (1)	–	Absent	Present (42 days)	–	1 in 50	–	–
54	Pale brown and black (6)	–	Hæmolytic streptococcus	Present (42 days)	+	1 in 125	–	–
55	Light brown (3)	–	Absent	Present (21 days)	–	1 in 25	–	–
56	Dark brown. Gallbladder and stones	Few gram-+ve cocco-bacillary forms	Absent	Present (46 days)	–	1 in 50	–	–
57	White (1)	–	Absent	Present (19 days)	–	1 in 50	–	

* Negative result indicates presence of species with similar characteristics and absence of another species

ABLE II—NUMBER OF LAYERS IN 57 SPECIMENS OF GALLSTONES AND PRESENCE OF ACTINOMYCES (CULTURE) IN EACH TYPE OF STONE

No of layers	No of stones	Actino positive (%)
Homogeneous	8	3 (*37 5*)
2	22	9 (*41*)
3	21	12 (*57*)
4—	6	6 (*100*)
Total	57	30 (*52 6*)

Though the number of gallstones containing four or more layers is small, seems that as the number of layers increase, so do the chances of isolating tinomyces

Commentary on Chemical and Bacteriological Findings

hemistry

Analysis of the whole stone (table III) and the centre of the stone (table IV) confirmed the presence of recognised onstituents of gallstones It also showed that no one onstituent, particularly cholestrol and bile-pigment, is lominant Rovsing's theory—that bile-pigment is at the entre of every gallstone—did not seem to be upheld by he analysis But 8 stones in which pigment was not letected by Foucet's test did show a macroscopic disolouration of the centre The nature of this residual igment has still to be defined It may correspond to that imilar residual pigment named bilihumin by earlier nvestigators (Stadeler, cited by Hammarsten 1914)

ABLE III—OVERALL ANALYSIS OF 57 SPECIMENS OF GALLSTONES AND ANALYSIS OF 30 STONES CONTAINING ACTINOMYCES

Substance	Analysis of 57 stones (%)	Analysis of 30 actino-stones (%)
rotein	49 (*86*)	25 (*83*)
holesterol	47 (*82*)	22 (*73*)
ile-pigment	45 (*79*)	25 (*83*)
arbonate	46 (*81*)	24 (*80*)
Calcium	20 (*35*)	13 (*43*)
Phosphorus	14 (*25*)	6 (*20*)
Iron	7 (*12*)	3 (*10*)

The analysis is of special interest in showing that protein and carbonate merit as much study as cholesterol and bile-pigment Martensson (1941) also drew attention to the presence of protein and cites Lichtwitz as showing that cholesterol can be precipitated by albumen In view of recent interest in the phenomenon of chelation in relation to the initiation and growth of calculi (Boyce et al 1955), the protein may bear a special relationship to the calcium present Yet the results of this analysis show that the occurrence of calcium does not correspond with that of protein, and neither with bile-pigment nor even carbonate, though conjugation with any of these is to be expected Carnot and Gruzewska (1928) declared the presence of an abnormal protein, cholenuclein, in the bile of cholecystitis and cholelithiasis This was said to be related to organ nucleoproteins and was possibly the result of epithelial cell destruction

Bacteriology

Rosenow (1914) examined the centre of 30 gallstones In 25, streptococci were isolated, in 5, *E coli*, in 1, *B typhosus*, in 2, *E coli* and *B welchii* Illingworth (1927) examined 23 stones, finding 7 infected (2 with streptococci, 3 with *E coli*, and 2 with staphylococci) Rosenow and Illingworth had, in addition, examined the walls of 29 and 100 gallbladders respectively Rosenow isolated streptococci in 21 and *E coli* in 10 Illingworth found streptococci in 34, *E coli* in 3, and staphylococci in 2 It is difficult to postulate why, in that period of years, the streptococcus was the organism to be isolated by these and several investigators, why, in the last decade of the nineteenth century *B typhosus* and *E coli* were often isolated According to Cushing, Flexner found typhoid in 50% of cases of cholecystitis, and Gilbert and Fournier had even classified biliary lithiasis into two groups lithiasis due to *E coli* and lithiasis due to *B typhosus* Perhaps the variance in the bacteriological findings is a reflection of the changes in disease incidence over the passage of time, typhoid fever was declining in incidence at the beginning of this century but diseases attributable to the streptococcus were prevalent up to the chemotherapeutic era

TABLE IV—ANALYSIS OF CENTRE OF 57 SPECIMENS OF GALLSTONES (HOMOGENEOUS STONES INCLUDED), AND ANALYSIS OF 30 STONES CONTAINING ACTINOMYCES

Substance	Analysis of 57 stones (%)	Analysis of 30 actino-stones (%)
Protein	37 (*65*)	18 (*60*)
Cholesterol	43 (*75*)	20 (*66*)
Bile pigment	42 (*74*)	23 (*76*)
Carbonate	33 (*58*)	15 (*50*)
Calcium	14 (*25*)	10 (*33*)
Phosphorus	11 (*20*)	6 (*20*)
Iron	5 (*10*)	2 (*6*)

Of the 57 stones examined in this series, *E coli* were found in 4, a streptococcus in 2, and a staphylococcus in 8 But the finding of actinomyces in 30 stones was quite unexpected Further, the serological tests indicate this species is not the actinomyces of Wolff and Israël

A further, though complex, extension of such an investigation would therefore be concerned with the old theory of blood-borne spread from a focus of infection, and such a source could be the mouth Martensson cites Naeslund (1925) among others as bringing actinomyces into prominence with regard to pathology of salivary and dental calculus, and he discusses the role such an organism may play in producing the calcified stone of such concretions and scales

Correlation Between Chemical and Bacteriological Findings

Naeslund considered that the mycete caused the precipitation of calcium salts in a colloid solution Citron (1945), in this context, demonstrated the alkaline phosphatase activity of the *Actinomyces israeli* and showed that the precipitation of calcium only occurs in a solution which contains organic phosphate Certainly, dental tartar and salivary calculi contain a large amount of calcium phosphate (76%) (Glock and Murray 1938) Tables III and IV show that in this investigation there is no significant difference between those stones or stone centres which contained actinomyces and those which did not Unlike salivary calculi, carbonate and not phosphate is dominant in gallstones Thus any further elucidation of this problem will involve further analyses, bacteriological, chemical, and extensive serological techniques

Summary

The early theories, chemical and bacteriological, of the cause of gallstone formation are outlined Research into the reproducibility of previous findings, as part of a wider programme of investigations, led to a study of whole and central portions of 57 specimens of gallstones by qualitative chemical analysis and the bacteriological methods of direct smear, culture and serology

An actinomyces was isolated from 30 of the 57 specimens The serological character of each organism indicates the presence of a species distinct from *Actinomyces bovis* The findings of previous investigators were not confirmed and a possible explanation is given

Chemical analysis did not confirm any dominance of cholesterol or bile-pigment especially in the centre of the

stones and shows that protein and carbonate deserve as much attention There is no apparent difference in the stones that did and did not grow actinomyces

The old theory of blood-borne infection causing a gall-bladder lesion and calculus formation from a distant focus, such as the mouth, is reintroduced with reference to a species of actinomyces found in oral concrements

An indication is given of the uses of serology and bacteriological chemistry (with respect to protein and inorganic constituents) in the furtherance of such research

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INOPERABLE CANCER OF THE BRONCHUS TREATED BY MEGAVOLTAGE X-RAY THERAPY

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IN a previous article (Morrison and Deeley 1957) we gave a preliminary report of the results of treatment of inoperable carcinoma of the bronchus by megavoltage X-ray therapy We described the palliative benefits, and gave the one-year survival-rate in a group of 199 patients We now report the later progress of the same group, with an additional 78 patients treated since 1957

The Patients

All the patients treated had a carcinoma of the bronchus, which was considered inoperable either because of advanced local disease or because the respiratory reserve was insufficient to allow lung resection to be performed We considered these patients were suitable for a course of radiotherapy aimed at curing the disease, because they were still in reasonably good general health, with no clinical evidence that the disease had spread outside the chest Patients who had had a previous operation on the chest, apart from an exploratory thoracotomy, were excluded from the series Of the 277 patients who completed a radical course of treatment, 257 (93%) were men and 20 (7%) were women

Attempts were made to obtain histological proof of the diagnosis either by biopsy at the time of bronchoscopy or, in peripheral tumours, by drill biopsy through the chest wall In 7 patients the clinical diagnosis was confirmed by isolation of malignant cells from the sputum In 18 patients (17%) histological confirmation was not obtained, the diagnosis of carcinoma being based on the clinical and radiological findings

The histological types of the 277 tumours treated were

Squamous	135
Anaplastic and oat-celled	73
Adenocarcinoma	5
Malignant cells in sputum	7
Carcinoma of unspecified type	1
No histology or negative histology	[illegible]

The main site of involvement of the primary tumours is shown in table I 1 patient had bilateral lesions involving the right middle lobe and left upper lobe, we regarded these as separate primary tumours and each received radical treatment

TABLE I—SITE OF THE PRIMARY TUMOURS

Left			Right				Bi lesio
Main bronchus	Upper lobe	Lower lobe	Main bronchus	Upper lobe	Lower lobe	Middle lobe	
35 *(12 7%)*	66 *(23 9%)*	44 *(15 9%)*	29 *(10 4%)*	64 *(23 2%)*	34 *(12 3%)*	1 *(1 4%)*	1
Total = 145 (52%)			Total = 131 (48%)				1

We attempted to divide the cases into two groups patients with and patients without evidence of lymph-node involvement of the mediastinum The evidence for mediastinal node involvement was based on the clinical, radiological, bronchoscopic, or thoracotomy findings Table II gives the incidence of involvement, and shows that anaplastic tumours have a higher rate of node involvement than squamous-cell tumours A similar finding was reported by Hinson (1958)

Treatment

The treatment was given by an 8-million-volt linear accelerator installed by the Medical Research Council at Hammersmith Hospital The physical characteristics of the X-ray beam produced by this machine, and the clinical advantage of megavolt compared with 240 kV radiation have been discussed (Morrison, Newbery, and Deeley 1956) The greater energy of megavolt X-rays enables the tumour to be given higher doses of radiation with fewer harmful effects to the skin and subcutaneous tissues, and with a lower total-body dose Hence, both the local and general radiation reactions after megavoltage therapy are less than after 240 kV therapy

The treatment was planned to give a mean dose to the tumour of 4500 rad units in four weeks by daily exposures When a very large field had to be used, and a greater volume of tissue was irradiated, the dose was reduced to 3600 rads Nearly all the patients were able to tolerate the whole course, and few had any of the disturbing reactions often associated with radiation therapy

The region irradiated included the area of tumour opacity as seen in posteroanterior and lateral radiographs, with a z

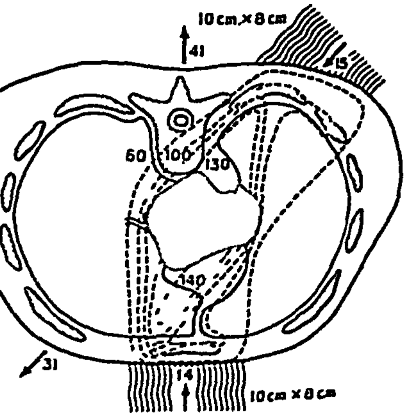

Fig 1—Cross-section of chest, showing position of fields and distribution of radiation

BLE II—THE EXTENT OF THE PRIMARY TUMOUR IN THE TWO MAIN HISTOLOGICAL TYPES

—	Squamous	Anaplastic
o mediastinal involvement	57 (*42%*)	24 (*31%*)
idence of mediastinal involvement	78 (*58%*)	54 (*69%*)
Total	135	78

f 2 cm of apparently normal lung surrounding the opacity d the mediastinal-node areas Because of the sharp definition the beam, it was possible to avoid irradiating the spinal rd and to spare the opposite lung as much as possible by a mple arrangement of two fields (fig 1)

Before starting the radiotherapy most of the patients were dmitted to hospital for treatment to improve their general ealth, and to treat any associated infection in the lung

Results

The *relief of symptoms* by this treatment has been iscussed in our previous article Hæmoptysis was rrested in 94% of cases, and about 75% of patients with lyspnœa, pain, or cough were also relieved The alliation did not differ in the squamous and anaplastic ypes of growth

The *survival-rates* have been calculated by the life-able method Fig 2 shows the yearly survival for all the atients for five years after treatment, and it will be seen hat 6% lived for five years or more After three years the isk of dying from the disease is small, and a three-year survival-rate seems to give a satisfactory index of the value of the treatment in curing or controlling this disease

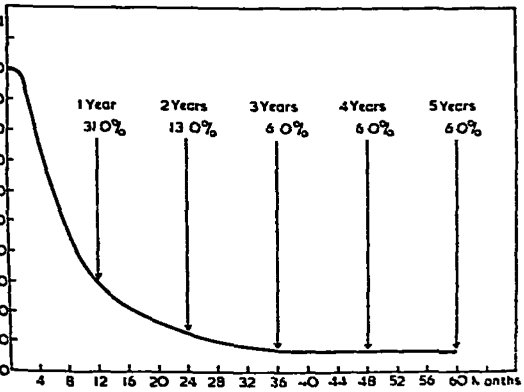

Fig 2—Survival curve after treatment of carcinoma of the bronchus.

In table III the results are analysed according to the histological findings In squamous-cell tumours the three-year survival-rate was 8 9%, but only 1 patient (1 5%) with an anaplastic-cell tumour survived for three years This table also shows that the chance of survival is best (10%) in squamous-cell tumours with no evidence of mediastinal spread

The cases were divided into three groups according to whether the tumour arose in the main bronchus, the upper-lobe (including the middle-lobe) bronchus, or the lower-lobe bronchus As there was no significant difference in the distribution of the histological types or in the incidence of mediastinal spread at the three sites, it was possible to compare the effect of the site of origin on the survival-rate Table IV shows that the prognosis is significantly better for patients with upper-lobe (and middle-lobe) tumours than for patients with lower-lobe tumours The same difference in the survival-rates between tumours of the upper and lower lobes was found in patients treated with 240 kV X rays (Brown 1952), and in those who had a resection (Carlisle et al 1951, Bignall and Moon 1955)

Other Reported Results

The survival-rates which have been reported in inoperable carcinoma of the bronchus up to five years after treatment by radiotherapy are shown in table V. These range from 2% to 10% at three years One cannot compare these results or the techniques employed without knowing the method of selection of the patients for treatment, the distribution of the histological types, and other factors known to affect prognosis

TABLE III—RELATION OF HISTOLOGICAL FINDINGS, MEDIASTINAL SPREAD, AND SURVIVAL-RATES

—	Squamous			Anaplastic		
Spread	All cases	Without mediastinal spread	With mediastinal spread	All cases	Without mediastinal spread	With mediastinal spread
3-year survival	8 9%	10%	7%	1 5%	0%	2%

TABLE IV—EFFECTS OF THE SITE OF THE PRIMARY TUMOUR ON THE 3-YEAR SURVIVAL-RATE

—	Main bronchus	Upper and middle lobes	Lower lobe
No of cases	63	134	80
3-year survival	*5%*	*9%**	*2%**

* The difference between these results is statistically significant.

Comparison with Patients Treated with 240 kV X Rays

As we mentioned in our previous article, very few patients having megavoltage therapy suffer from the constitutional effects of the radiation, and the only troublesome local effect is mild dysphagia in a small proportion of them Because of the diminished reactions, larger tumours can be treated with megavoltage therapy than with conventional deep X-ray therapy, and megavoltage radiation can therefore be used in the treatment of patients who formerly would have been unsuitable for radical treatment

In a group of 176 patients treated with 240 kV therapy at this hospital between 1949 and 1953, the three-year survival-rate was 2%

Table VI shows the survival-rates for 240 kV therapy compared with 8-million-volt therapy in the squamous and anaplastic tumours Although more advanced cases were included in the group treated at the higher energy, the survival-rates are slightly better for squamous-cell

TABLE V—RECENT REPORTS OF SURVIVAL-RATES AFTER RADICAL-RADIATION TREATMENT

Report	No of cases	Energy of radiation	Tumour dose	% proved	% survival (yr)				
					1	2	3	4	5
Hilton and Pilcher (1955)	203		4000–5500r	63	27	11			[illegible]
Schulz (1957)	385	250 kV	4000r		15	5	3	1	1
Smithers (1955)	171	240 kV	5000–7000-	60	37	13	9	5	[illegible]
Krabbenhoft and Leucutia (1958)	132	2 MeV and 250 kV	Various	100	12	8			2
Shanks (1959)	136	240 kV	4000r		31	15	10	3	2
Hammersmith Hospital (1949–53)	176	240 kV	3250–4000r	61	24	11	2		
Present series (1953–58)	277	8 MeV	[illegible]500 rads	53	30	14	7	5	6

TABLE VI—COMPARISON OF SURVIVAL-RATES AFTER 8-MeV AND 240-kV X RAYS

—	Squamous		Anaplastic	
Therapy	8 MeV	240 kV	8 MeV	240 kV
No of cases	138	68	78	45
Survival				
1 year	38.0%	21.2%	15.2%	15.5%
2 ,,	18.4%	16.5%	6.0%	6.6%
3 ,,	8.9%	1.5%	1.5%	0%

lesions The results of treatment for the two methods differ little in the anaplastic-cell tumours

Indications for Radical Treatment

As a result of treating this series we have formed an idea of the type of patient likely to benefit from radical megavoltage therapy We now consider that this is indicated in patients with inoperable disease who are not severely debilitated, who have no evidence of spread outside the chest, and who have the squamous-cell type of tumour When the lesion is of the anaplastic or oat-cell type the chance of survival is very poor, and there seems to be less justification for subjecting the patient to a long course of radiation therapy Short courses of treatment, however, may be given to relieve distressing symptoms In patients with chronic bronchitis, or other chronic inflammatory disease, the radiation reactions are more severe than in lungs unaffected by previous disease, and it is often impossible to give a sufficient dose of radiation to eradicate the growth The radiation may also aggravate the cough and increase the quantity of sputum

A serous pleural effusion does not always indicate pleural involvement by growth, but an effusion which contains blood or malignant cells suggests a widespread intrapleural dissemination which cannot be adequately treated

Discussion

Failure to cure carcinoma of the bronchus can be attributed to incomplete response of the primary growth to the radiation, or to early dissemination of tumour cells outside the treated area At the time of treatment some patients may already have distant metastases which cannot be detected clinically A number of tumours, however, do not disseminate widely, and even at death are still confined to the chest

The extent of the disease, macroscopically, in 31 cases at postmortem was

	Anaplastic	*Squamous*
No of cases	11	20
Spread outside chest	7 (*63%*)	7 (*35%*)
No spread outside chest	4 (*37%*)	13 (*65%*)

In 176 patients who were examined regularly after treatment until the time of death, a similar proportion showed no sign of spread

	Anaplastic	*Squamous*
No of cases	71	105
Clinical signs of disease outside the chest	52 (*73%*)	34 (*32%*)
No signs of disease outside the chest	19 (*27%*)	71 (*68%*)

These findings represent the extent of the disease terminally, but, if one assumes that any dissemination which becomes evident later will already have occurred at the time of treatment, there are roughly 2 out of 3 patients with squamous lesions, and 1 out of 3 patients with anaplastic lesions in whom the tumour is apparently still confined to the primary site and who are potentially curable In about half the patients treated, therefore, the disease could probably be cured by effective local treatment

The dose of radiation which may be given to any tumour is limited by the tolerance of the surrounding normal tissues, and in the majority of cases this dose appears to be insufficient to destroy the tumour co pletely With high-energy radiation, a relatively grea tumour-to-normal-tissue dose ratio is possible than w 240 kV X rays, permitting a slightly higher tumour do to be given with less damage to the normal tissues W a further increase of radiation energy, however, it see unlikely that this ratio will increase any further

Summary

277 patients with inoperable carcinoma of the bronch have received radical treatment with megavoltage X ra The results of treatment and the survival rates are giv

With megavoltage therapy there are fewer system and local radiation reactions, making it possible to tr larger and more extensive tumours

The chances of survival are greater with squamo cell tumours (three-year-survival-rate 8.9%) than wi anaplastic-cell tumours (three-year-survival-rate 1.5%)

Radical X-ray treatment of carcinoma of the bronch (squamous-cell type) is indicated when the tumour inoperable in patients who are not severely debilitate and who have no evidence of spread outside the chest

Local X-ray treatment may fail because the prima growth responds incompletely, or because of ea dissemination of tumour cells

We should like to thank Dr C A P Wood, director of the MR Radiotherapeutic Research Unit, Dr L H Walter, and Dr P Woodyatt for referring their patients to us for treatment

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ACQUISITION OF STAPHYLOCOCCI BY NEWBORNS

DIRECT VERSUS INDIRECT TRANSMISSION*

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PATHOGENIC staphylococci acquired by newborn inf in hospital nurseries are responsible for a high inciden of minor diseases, such as impetigo and conjunctivi and a significant rate of more serious illnesses, such mastitis, septicæmia and pneumonia, which arise so

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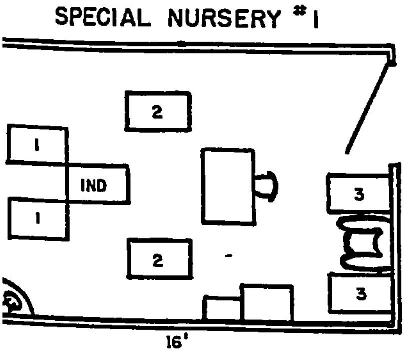
* These studies were sponsored by the Commission on Strepto Diseases of the Armed Forces Epidemiologic Board, a supported by the Office of the Surgeon General, Departm of the Army, Washington, D C

nths after discharge from hospital both in the in- ts and in members of their families The rates of quisition of these staphylococci by newborn infants ry from time to time, but, during periods of widespread semination of the organism to the infants, epidemics staphylococcal disease are common Such epidemics ordinarily well established by the time they are cognised, because the clinical manifestations usually not appear until after the infants have been discharged m the hospital Interruption of the epidemics is tempted by identification and removal of all possible man and environmental sources of the offending ganism—a procedure requiring complex and extensive cteriological surveys and techniques—or by continuous ophylactic administration of antibiotics to all infants he development of more rational methods to interrupt e spread of the organisms to the infants is hampered by ucity of information concerning modes of transmission staphylococci

The nurseries at this hospital have been the sites of demic and intermittently epidemic staphylococcal sease for several years The usual methods of control ve resulted in only temporary amelioration The resent study represents a preliminary effort to define e important modes of transmission so that methods for ntrol of these infections may be developed The study as designed primarily to determine whether infant-to- fant spread was direct (heavy droplets projected short stances) or indirect (airborne droplet nuclei or dust)

Method

A small room, 11 by 16 ft, was employed as a special ursery (see figure) Circulation of air was maintained by a n. An "index" infant, known to be a nasal carrier of a bacteriophage-typable strain of staphylococci, was placed in a bassinet at one end of the room New-born infants were admitted directly from the delivery room to 1 of 6 bassinets set at fixed distances from the index baby, and were etained in these bassinets without removal for forty-eight ours 2 of these bassinets (position 1) were placed immediately djacent to the index baby, 2 (position 2) at a distance of $4^1/_2$ ft, nd 2 (position 3) at 11 ft. The 6 infants were cared for by staff of the same three nurses working in eight-hour shifts These nurses wore masks which were changed frequently On entering the nursery they scrubbed their hands and arms for three minutes with 'Phisohex' and washed with the same preparation between contacts with different infants The index baby was observed but not touched by these nurses and administered to only when necessary by outside personnel summoned by the special nurse All other persons were excluded After forty-eight hours of exposure to the index baby, each infant was removed to the main nursery and another study infant was admitted A different index infant was employed each week. It was anticipated that, if airborne droplet nuclei had a major role in transmission, organisms should be acquired at random in all bed positions Organisms spread directly by heavy droplets should appear predominantly in infants located near the index baby



Plan of study nursery

Cultures of the anterior nares of each study infant were procured twice daily for four days (including the forty-eight hours in the special nursery) and daily thereafter until discharge, usually on the fourth day Cultures were obtained from 57% of the infants three to six weeks after discharge The anterior nares of all involved personnel were cultured twice weekly Swabs were inoculated on to mannitol agar plates containing 7% salt, which were incubated at 37°C for forty-eight hours Two to four mannitol-fermenting colonies were picked from each positive plate for bacteriophage typing An infant was considered to have acquired an organism if it was recovered repeatedly or if it appeared in profusion on the final culture

Findings

48 infants were exposed to index babies carrying strains of staphylococci whose bacteriophage-typing characteristics were clearcut and reproducible (types 80/81 and 3B/3C/71) An organism identical to that of the index baby was acquired by only 1 infant, he was in a bassinet immediately adjacent to the index infant 43 babies were exposed to index infants carrying strains whose bacteriophage-typing characteristics were somewhat variable (7/47/53/54/75) 7 of these babies acquired organisms whose typing patterns were similar, but not identical, to those of the index baby's strain The source of these organisms could not be determined with certainty Two of these strains differed only slightly, and therefore were probably the same as that of the index infant, both of these infants were located in bassinets at position 1 The patterns of five other strains were less similar but nonetheless impossible to differentiate from the index strain, and accordingly were considered to be possibly the same 1 infant was at bassinet position 1, and 2 each at positions 2 and 3

In contrast to the relatively low rate of spread from infant to infant, there was a high rate of acquisition of organisms of bacteriophage types identical to those carried by two of the three special nurses (The third nurse exhibited repeatedly negative cultures) 21 of 95 infants acquired a strain carried by nurse A (80/81/52/52A), and 12 babies acquired the strain of nurse B (3A/3B/3C) When it became apparent that the infants were being infected predominantly by the organisms carried by the nurses and not those of the index babies, nurse A was relieved of all active duties during the fifth and sixth weeks of the study, but she was required to spend each of her eight-hour shifts unmasked and seated in a chair between (and immediately adjacent to) 2 study bassinets She resumed her full duties wearing a mask during the final two-week period of the study The accompanying table shows that nurse A's organisms failed to appear in any infants who were exposed to her during the fifth and sixth weeks of the study, but her strain again reappeared during the final two weeks Nurse B worked overtime in the nursery to accomplish nurse A's duties during the two weeks that nurse A sat in the chair, it was at this time that her type appeared more frequently in the exposed infants

ACQUISITIONS OF STAPHYLOCOCCAL STRAINS CARRIED BY NURSES

Weeks of study	Infants		
	No exposed	Acquisitions	
		Nurse-A type	Nurse-B type
1–2	24	11	1
3–4	23	4	0
5–6	24	0*	7
7–8	24	6	4
Totals	95	21	12

* During weeks 5–6 nurse A sat in room, unmasked, without touching infants

The results of this study suggested that personnel-to-infant spread of staphylococci was of relatively greater importance than infant-to-infant airborne spread, and that handling of the infants was required for such personnel-to-infant transmission A subsequent study has confirmed that spread of a carrier's organism to newborn infants does occur by handling alone In this study infants were admitted to an 'Isolette' incubator directly from the delivery room This incubator is a closed, heated unit to which outside air is pumped via a hose from an outside window Access to the infant is afforded by portholes which permit entry of the hands and forearms of the nurse Thus spread of organisms from personnel to infant is unlikely except by hand-to-infant transmission

37 infants were placed in the incubator shortly after birth by personnel known to be free of staphylococci One of 3 "index" nurses then administered "initial care", consisting of washing the infant with cotton balls and water, taking the rectal temperature, combing the infant's hair, and dressing the infant The hands of the nurses were not washed immediately before handling the infant Each of these index nurses carried in the anterior nares a different bacteriophage type of staphylococci (80/81, 80/81/52/52A, and 3A/3B/3C) Each infant was exposed on this one occasion and was then placed in the main nursery, where there were no personnel carrying staphylococci of types similar to those of the index nurses 20 (54%) of the 37 infants acquired the strain of the appropriate nurse after this sole exposure, as determined by umbilical and nasal cultures

Conclusion

The results of these studies indicate that personnel-to-infant spread of organisms has a major role in the dissemination of staphylococci in nurseries for the newborn, and that this spread is predominantly from the hands of the carrier to the infant Spread from infant to infant by the airborne route appears to be of lesser importance Further studies of means by which this dissemination from personnel to infant may be interrupted are in progress

This study was made possible by the complete cooperation of the department of nursing and especially of Miss Phyllis Fischer, R N, Miss Dorfetta Griffin, R N, Mrs Norma Jenkins, R N, and Mrs Shirley Hill, P N We thank Mrs Norma Brunk for technical assistance

EFFECT OF THE SULPHONYLUREAS ON FIBRINOLYSIS

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IN the study and treatment of thromboembolic disease much attention has been paid to the obverse side of the coin, coagulation, the reverse side, fibrinolysis, may be equally important There are two possible approaches to the use of fibrinolysis as a therapeutic agent First we might activate plasminogen, by the intravascular injection of either streptokinase or the "activator" which is thought to be produced when serum is treated with streptokinase This is being extensively tried in the U S A Secondly we might enhance the natural fibrino mechanism pharmacologically (Fearnley 1960)

A biphasic response of blood fibrinolytic activity t single injection of insulin has been reported in diabe consisting of an initial reduction in parallel with blo glucose levels, followed by a rebound increase at blood-glucose levels (Fearnley, Vincent, and Chakrab 1959) This suggested that the sulphonylurea co pounds, by lowering blood-glucose levels, might incre blood-fibrinolytic activity in non-diabetic subjects T conjecture has proved correct, but the observed increas fibrinolytic activity is not directly related to hy glycæmia, *some other mechanism may be responsi* We here report the effect of tolbutamide or chlorpro mide in eight arteriosclerotic inpatients

Patients and Methods

The patients were one woman and seven men suffer with arteriosclerotic disease of the heart or limbs, had status anginosus, and six had intermittent claudicati Fasting blood was obtained daily (except Sundays) bef the patient got up, at 8 A M ±15 minutes, for measu ment of blood fibrinolytic activity and blood-gluco After a control period of 4–6 days the patients were gi either tolbutamide or chlorpropamide in the doses stat the former was given in divided doses and the latter single dose at 9 P M

The fibrinolytic activity of the blood was measured by method of Fearnley et al (1957) The results are expresse lysis-times in hours, and are the means to the nearest h hour of duplicate determinations Readings were not m beyond 24 hours, so that all lysis-times of greater duration expressed as 24 hours When necessary the photogra modification of Lackner and Goosen (1959) was employ As blood-fibrinolytic activity and lysis-time are inver related, a decrease of lysis-time signifies an increase fibrinolytic activity and vice versa Blood-glucose measured by the method of Folin and Wu, the blood sam being collected in fluoride tubes and the determinations m within 3 hours of collection

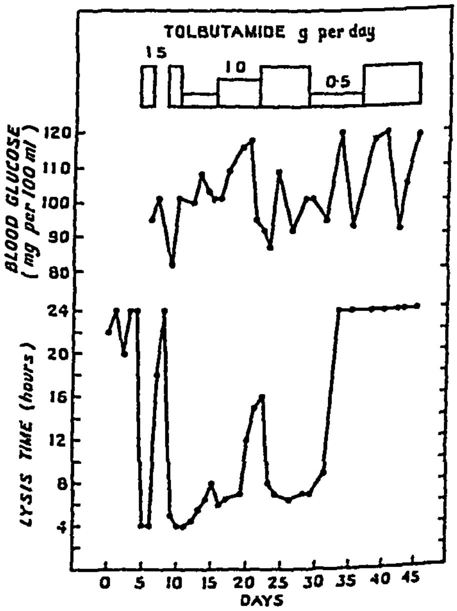

Fig 1 (case 1)—Increase of fibrinolytic activity by tolbutamide a woman with status anginosus.

Blood-clot lysis-times in hours and blood-glucose levels in mg 100 ml Blood fibrinolytic activity varied with the dosage of the to which the patient eventually became resistant

Serum-cholesterol was measured at intervals, but as) significant change took place the figures are not given

Results of Treatment

Case 1 (fig 1) —Woman, aged 69 Effort angina for 4 ars Admitted with acute coronary insufficiency and treated r 3 weeks with anticoagulants Severe pain at rest and on ight exertion kept her confined to bed, and 3 months after imission she was given tolbutamide Mean control lysis-me, 22 8 hours Tolbutamide 500 mg t d s was followed ithin 24 hours by a reduction of lysis-time to 4 hours The ug was stopped after 48 hours, and the lysis-time increased 18 and 24 hours Tolbutamide 500 mg t d s was then -started, and again the lysis-time fell to 5 hours Fig 1 iows that the lysis-time reflected alterations of dosage, and iat she eventually became resistant, the lysis-time reverting 24 hours Within a few days of receiving tolbutamide the verity of her pain diminished, and within 2 weeks she was ee from pain at rest She remained free of pain for a further 6 weeks when another attack of acute coronary insufficiency was followed by congestive failure from which she died

Case 2 —Man, aged 57 Intermittent claudication of left leg for 2 years, worsening recently Right leg similarly affected for a month Pain after walking 15-20 yards Pulsation absent in left dorsalis pedis and posterior tibial arteries Mean control lysis-time, 5 4 hours On tolbutamide 500 mg t d s, the lysis-time was reduced to 2 5 hours and during the next 20 days varied between 2 5 and 3 5 hours The patient was discharged on tolbutamide 500 mg t d s, and when last seen 2 months after discharge from hospital, could walk 1–2 miles without pain

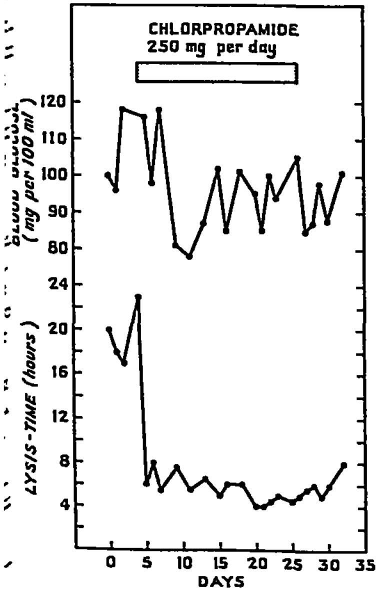

Fig 2 (case 3)—Increase of fibrinolytic activity by chlorpropamide in a man with status anginosus

Case 3 (fig 2) —Man, aged 55 Status anginosus for 4 months before admission, confining him to bed Electrocardiogram no evidence of infarction, conspicuous ST depression Mean control lysis-time 20 3 hours Given chlorpropamide 250 mg o d. for 23 days On the day after the start of the drug, the lysis-time dropped to 6 hours, and over the next 14 days it fell stepwise to 4 hours On the 5th day of treatment, his pain ceased After 10 days he was up and about, and he has remained symptom-free on moderate activity for $2^{1}/_{2}$ months 6 weeks after discharge he was readmitted for 4 days for lysis-time measurements which varied between 5 and 6 hours His lysis-time has, therefore, remained rapid, in spite of discontinuing the chlorpropamide.

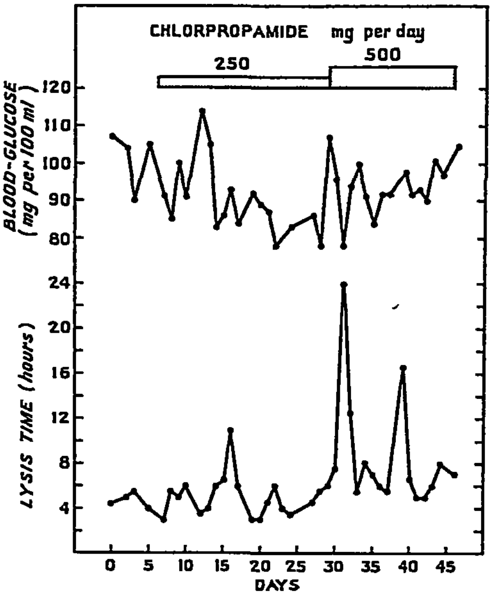

Fig 3 (case 6)—Decrease of fibrinolytic activity by chlorpropamide when dosage was raised to 500 mg daily in a man with intermittent claudication

Case 4 —Man, aged 51 Intermittent claudication of left leg for 2 years Pain after walking 10–50 yards Left foot colder than right Both dorsalis pedis pulsations absent Left posterior tibial pulsation barely palpable Mean control lysis-time, 18 5 hours After tolbutamide 500 mg b d, t d.s, and q d s the lysis-time fell only temporarily After chlorpropamide 250 mg b d it fell to 5–$7^{1}/_{2}$ hours with steady improvement of symptoms When he was readmitted 9 weeks after starting chlorpropamide his lysis-times were 5–8 hours ' Now after 4 months on chlorpropamide, he can walk several miles without pain He continues to take 250 mg o d

Case 5 —Man, aged 68 Intermittent claudication for 3 years Began in left leg, for which 2 years before admission a left lumbar sympathectomy had been done with moderate benefit Shortly after the operation he developed claudication in the right leg At the time of admission he was able to walk 50 yards before halting from pain in right leg Dorsalis pedis and posterior tibial pulsations absent in both legs Mean control lysis-time, $5^{1}/_{2}$ hours Given chlorpropamide 250 mg daily After 14 days the lysis-time was 2–3 hours He was discharged on the above dose, but at follow-up $2^{1}/_{2}$ months later he was no better, in that although his right leg had improved he was now halted at the same distance as before by pain in the left leg

Case 6 (fig 3) —Man, aged 66 Intermittent claudication of both legs for 18 months Pain after walking 200–300 yards Both posterior tibial pulsations absent Mean control lysis-time, 4 8 hours Chlorpropamide 250 mg daily was followed by a transient increase of lysis-time, and after 24 days the dose was increased to 500 mg daily After this, the lysis-time immediately increased, and the mean level over the next 18 days was 9 0 hours This patient showed no symptomatic improvement, and chlorpropamide in a dosage of 500 mg daily appeared to result in a definite increase of lysis-time and hence a reduction of blood fibrinolytic activity during the period of observation.

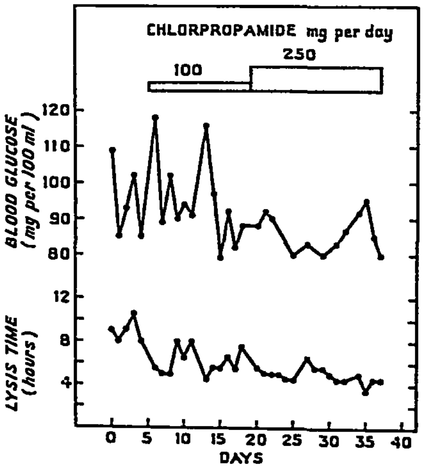

Fig 4 (case 7)—Increase of fibrinolytic activity by chlorpropamide in a man with arteriosclerotic gangrene.

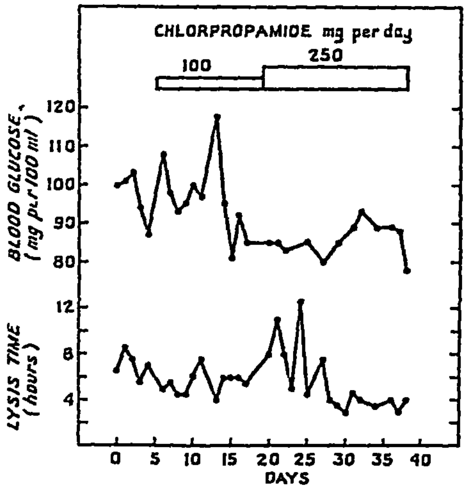

Fig 5 (case 8)—**Biphasic effect on fibrinolytic activity by chlorpropamide in a man with intermittent claudication.**

When dosage was increased from 100 mg to 250 mg daily, the lysis-times were prolonged for 10 days, and then were reduced below the control levels

Case 7 (fig 4) —Man, aged 52 Early gangrene of toes of right foot with rest pain 2 years before admission an above-knee amputation had been done for gangrene following embolism of the left popliteal artery Since then increasing claudication of right leg, halting him at 20 yards Popliteal and foot pulses absent on right ischæmic cyanosis of toes extending on to dorsum of foot Mean control lysis-time, 9 hours Chlorpropamide 100 mg daily for 14 days was followed by a mean lysis-time of 6 hours The dose was then increased to 250 mg daily and during the next 18 days the mean lysis-time was 4 9 hours During treatment his rest pain has diminished in frequency and there has been a definite reduction in the extent of ischæmic cyanosis, which is now confined to the distal halves of the toes

Case 8 (fig 5) —Man, aged 53 Intermittent claudication of left leg for a year, steadily worsening Before admission pain halted him at 100 yards Dorsalis pedis and posterior tibial pulsations absent on left Mean control lysis-time, 7 hours Given chlorpropamide 100 mg daily for 14 days, during which period the mean lysis-time was 5 5 hours The dose was then increased to 250 mg daily, and this was followed by an increase of lysis-time for 8 days (mean lysis-time *8 hours) The lysis-time then fell for the ensuing 11 days* (mean lysis-time, 3 7 hours) During the latter period, the patient's walking distance has increased from 100 to 400 yards and the pain has been less severe

Comment

Of three patients given tolbutamide, one (case 1) showed a prompt increase of fibrinolytic activity and temporary symptomatic improvement, but became resistant to this drug, one (case 2) showed increased fibrinolytic activity and sustained improvement, and one (case 4) showed an inconstant fibrinolytic response, and was transferred to chlorpropamide, which was followed by increased fibrinolytic activity and symptomatic improvement

Of six patients given chlorpropamide, two (cases 3 and 4) showed increased fibrinolytic activity and sustained improvement, both of which continued in case 3, in spite of cessation of the drug, two (cases 7 and 8) showed increased fibrinolytic activity, and to date improvement which can be classed as moderate, one (case 5) showed increased fibrinolytic activity but no improvement, and in one case (case 6) the drug appeared to reduce fibrinolytic activity

Discussion

An oral means of enhancing spontaneous fibn has not hitherto been described. Though both t amide and chlorpropamide appear capable of incre the fibrinolytic activity of the blood, their mode of is unknown As there is no obvious correlation betw the blood-clot lysis-times and blood-glucose levels, observed increase of fibrinolytic activity does not seem be a function of drug-induced hypoglycæmia It unlikely that nocturnal hypoglycæmia, causing release adrenaline, was responsible for the increased fibrinoly for had this been so one would expect at least some of fasting blood-glucose levels to be low Furthermore, patient experienced hypoglycæmic symptoms, these we specially inquired for and the blood-glucose levels we carefully watched because of the possible risk of se hypoglycæmia to arteriosclerotic patients

The magnitude of change in the lysis-times seems to related to the pre-treatment levels, since those patie with long lysis-times showed the greater change. To much should not be inferred from this, however, in th absence of knowledge about the relationship betwe lysis-time and fibrinolytic activity, which may not linear The reduction of lysis-time, which appears to influenced by dosage (cases 7 and 8), may take 2 weeks be fully manifest, as exemplified by case 3, where lysis-time showed an initial steep reduction followed a stepwise decrease over the next 14 days

In two of the patients, chlorpropamide appare increased the lysis-time This increase was followed b decrease below the control levels in patient 8, but not patient 6—possibly because the measurements were continued long enough The biphasic response of pat 8 is reminiscent of a similar response to an injection insulin in diabetics, and suggests the invocation of an posing mechanism which may subsequently be overco

Because of the resistance case 1 acquired to tolbutami the biphasic response of case 8, and the negative respo of case 6 to chlorpropamide, these results should viewed with caution They do not constitute suffici evidence for the indiscriminate therapeutic trial of th drugs in arteriosclerotic conditions But they do indic that the fibrinolytic activity of the blood can be influen by oral medication, and they are the first positive res from a number of pilot trials with various dr undertaken by one of us in the past five years The be haviour of chlorpropamide and tolbutamide mer further study (1) to determine whether either or both enhance fibrinolytic activity for a long enough time allow planned therapeutic assessment, and (2) to disco the frequency and duration of the negative effect enco tered with chlorpropamide, a potential disadvantage W would emphasise that diurnal variability, the known eff of exercise, and the possible effects of meals have made necessary to confine this study, and probably fur studies of these drugs, to inpatients, whose blood can b obtained fasting and under standard conditions of res

The investigation was designed to determine whether t sulphonylureas would increase the fibrinolytic activity the blood, rather than to evaluate any therapeutic bene which might ensue if this happened The data are to few to permit clinical conclusions Nevertheless, th improvement shown by some of the patients is not d couraging when taken in conjunction with the empir observations of Singh and Bardhan (1959), who hav reported improvement in 21 patients with angina pecto on tolbutamide 500 mg given nightly

Summary

The oral exhibition of tolbutamide or chlorpropamide is followed by increase in the fibrinolytic activity of the ood (taken when fasting) in seven of eight arteriosclerotic tients Of three given tolbutamide, one became resistant d another failed to respond, though he afterwards sponded to chlorpropamide Of six patients given lorpropamide, four showed increased fibrinolysis, one owed a biphasic effect consisting of a reduction of rinolytic activity followed by an increase above the ntrol levels, and in the sixth patient chlorpropamide emed to decrease fibrinolytic activity during the period observation

The increases of fibrinolytic activity could not be lated to the alterations of blood-glucose The magtude of change appears to be related to the control level fibrinolysis, since those patients with initially long sis-times showed the greater change

Six of the eight patients showed clinical improvement, hich was considerable in three and moderate in three

A means of enhancing spontaneous fibrinolysis by oral edication has not previously been described Further udy is required to determine whether the sulphonylureas ill be of value in arteriosclerotic diseases

We wish to thank Mr P M Birks for referring some of the tients with claudication and Miss Esther Gronow and Mr John ans for efficient technical assistance

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TOLBUTAMIDE IN THE TREATMENT OF THROMBOANGIITIS OBLITERANS

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THE relief of anginal pain with tolbutamide in March, 957 (Singh and Bardhan 1959), led to its trial in a case f thromboangiitis obliterans The patient suffered from urning and gnawing pain in both feet, and had œdema f the right foot with ulceration and gangrene of the big oe, together with glycosuria of toxic origin The result was a surprise Within a week, though the glycosuria was unaffected, the relief from pain was very striking and the spread of gangrene appeared to be halted Since then we have treated 36 cases of thromboangiitis obliterans with tolbutamide and, except in 2 cases of neuritic pain, the results have been consistently good

Material and Method

The patients were all Indian men, 25 to 42 years old, and the duration of their disease was two to seventeen years 24 were light to moderate smokers, but the others did not smoke In 17 cases, after temporary relief from preganglionic sympathectomy, symptoms had returned in full In 13 cases one or more limbs had already been amputated. According to their dominant clinical features, the cases could be grouped as follows

Group A (4 cases) —Intermittent claudication

Group B (5 cases) —Aching pains in the digits, instep, and ankle, intermittent claudication of moderate severity, lasting five to ten minutes, and coldness of extremities Erythromelia in 3 cases, superficial phlebitis with discoloration of skin in 2

Group C (3 cases) —Acute discomfort in the digits, instep, and ankle, more severe intermittent claudication lasting ten to thirty minutes, and coldness of extremities Superficial phlebitis with discoloration of skin in 1 case

Group D (7 cases) —Constant agonising burning or gnawing pain, coldness of extremities, and cyanosis of digits, in upper or lower, or both upper and lower limbs

Group E (12 cases) —Constant agonising burning or gnawing pain, coldness of extremities, œdema, and ulceration and gangrene in one or more digits, in upper or lower, or both upper and lower limbs

Group F (2 cases) —Paroxysmal lancinating pain in affected parts in patients with chronic disease

Group G (2 cases) —Pain and swelling of stumps in amputated cases

Group H (1 case) —Superficial phlebitis and pain and swelling of stump in an amputated case

Tolbutamide 0 5 g was given with breakfast, lunch, and dinner All previous treatment (e g, with nicotinic acid, ‘ Priscol ’, or α-tocopherol) was stopped, and, as pain and discomfort diminished, analgesics were tailed off, and eventually discontinued

When patients were free from symptoms, administration of tolbutamide was stopped so that the duration of relief without the drug could be assessed On return of symptoms, a second round of treatment was given, followed by continuous maintenance therapy with 0 5 to 1 0 g tolbutamide daily

As there was no difficulty in assessing the relief of severe pain needing strong analgesics (e g, pethidine and morphine) we did not use placebo controls in such cases In patients with less severe symptoms, however, in whom the buoyant effect of the drug on the mind may have influenced the results, placebo tablets were given both before and for four weeks after initial tolbutamide therapy Drug and placebo tablets appeared identical

Results

The patients felt improvement two to five days after starting tolbutamide therapy and were symptom-free before the fourth week was over Placebo controls were unaffected

The agonising rest pain which had driven many a patient to amputation, and at least one of them to attempted suicide, was relieved The relief was continuous and persisted throughout the day, surpassing in this way even the effect of repeated doses of morphine which had been given previously Similarly, intermittent claudication was relieved, the limiting factors were now overexertion and crippling from amputation Whether symptoms had recurred after sympathectomy, or whether gangrene was present, or whether response to analgesics, vasodilators, or α-tocopherol had been inadequate or nil, did not appreciably affect the benefit from tolbutamide Even the stump pain disappeared But the paroxysmal lancinating pain of neuritic origin, in 2 cases, did not respond

Though there was no immediate change in arterial pulsation which could account for this relief, there was some flushing of the skin and the extremities felt warmer Discoloration of skin, if present, disappeared and the accompanying superficial phlebitis subsided Moist gangrene was more easily and quickly demarcated than is usual in this disease, the associated swelling of the hand or foot rapidly subsided, and when the dead tissues in digits peeled off, although the bare phalanges were sticking out, the wounds were remarkably clean and tended to heal In 2 cases with glycosuria this had not happened with adequate insulin therapy, and the effect of tolbutamide did not seem to be related to its hypoglycæmic action

On discontinuing tolbutamide, relief of symptoms persisted for from one to seven weeks

The general condition of the patients improved they put on weight and were cheerful There were no side-effects

Illustrative Case

In June, 1957, a Hindu, aged 30, developed gangrene of both feet, following injuries After left lumbar sympathectomy in December there was a temporary halt, but below-knee amputation of the left leg had to be performed in August, 1958 Right lumbar sympathectomy was done in September of that year, and above-knee amputation of the right leg a month later Last December there was an acute flare-up in the right hand, with constant agonising pain, œdema, and gangrene of the thumb, index, and middle fingers, and glycosuria of toxic origin Pulsation was very feeble in the right radial artery but present in the right brachial artery, pulsation in the left arm was normal Though the glycosuria was fully controlled with insulin, this did not help the local condition When insulin was stopped and tolbutamide ('Rastinon') therapy was started on January 5, 1960, the pain diminished from the fifth day, by the sixteenth day he was symptom-free, the gangrene was demarcated, and œdema of the hand had subsided Later the dead tissues peeled off and the wounds were clean and dry, the phalanges, which were neatly sticking out, were removed Relief is maintained with tolbutamide

Discussion

We cannot yet explain the beneficial effect of tolbutamide in thromboangiitis obliterans The intermittent claudication of ischæmic origin, the burning and gnawing pain due to thrombosis, and the pain, tenderness, and discoloration associated with thrombosis of veins are relieved, but the paroxysmal lancinating pain of ischæmic neuritis is unaffected Similarly, in our experience, other pains of neuritic origin—e g, pain of diabetic and alcoholic neuritis, tabetic pains, sciatica, and root-pains of spinal tumours—are not relieved, but patients with hemiplegia and parkinsonism benefit to some extent A report by Gates and Hyman (1960) on the use of tolbutamide in paralysis agitans corroborates this

The drug seems to have an anti-inflammatory action, judging by the subsidence of pain, swelling, and inflammation in areas where there was no obvious increase in blood-supply In a case of rheumatic carditis, where low fever had persisted for several months in spite of salicylate and cortisone therapy, the temperature fell to normal within a week of starting tolbutamide, and the drug also controlled fever following severe measles In both cases, the fever returned when tolbutamide was discontinued (after the temperature had been normal for three days) but subsided again when the drug was administered again

On the analogy of the relief given by tolbutamide in angina pectoris (Singh and Bardhan 1959, Fabrykant and Ash 1960), it is likely that tolbutamide also prevents the local formation or accumulation of pain-producing metabolites

As one of the characteristics of thromboangiitis obliterans is remission and exacerbation, the effect of tolbutamide maintenance therapy cannot yet be assessed, but 3 cases in which the disease was rapidly spreading and which have been treated for over two years have shown continuous clinical remission

Summary

36 cases of thromboangiitis obliterans were tre with tolbutamide, 0 5 g thrice daily with meals Wi three to four weeks there was spectacular relief of in mittent claudication and rest pain in the 34 patients had these symptoms, but the neuritic pain of the 2 o patients did not respond When tolbutamide the was discontinued, relief persisted for one to seven we With maintenance therapy 3 cases have been in continu clinical remission for over two years

We are grateful to Mr G Winternitz of Hoechst Pharmac for supplies of 'Rastinon', and to Major-General C C K commandant of the Armed Forces Medical College, Poon permission to publish this paper

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THE XXX SYNDROME

FREQUENCY AMONG MENTAL DEFECTIVE AND FERTILITY

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As part of a wide investigation of chromatin-posit (XXY) Klinefelter's syndrome in Glasgow (Fergus Smith et al 1957, Stewart et al 1959) Ferguson-Sm (1958) surveyed most of the male population of Len Castle Mental Deficiency Hospital, and established t the frequency of XXY cases was rather over 1% Wh the description by Jacobs et al (1959, 1960) of th so-called superfemale with an XXX chromosome comp ment provided what seemed a feminine counterpart the genetic side to the XXY Klinefelter's syndrome seemed logical to institute a similar search for cases this type on the female side of the same mental deficie hospital

Investigation of the cases found has not yet b completed, but some points which have been alr established deserve report

Methods

Buccal mucosal smears were taken from as many as poss of the 637 female patients in the hospital, and 595 satisfac preparations have so far been examined These cases s to be a representative sample of the varieties of mental de seen in the majority of similar institutions in this cou although, owing to the policy of finding outside emplo for as many patients as possible, we have seen relatively of the highest grade of mental defectives

FINDINGS IN 4 CASES OF XXX SYNDROME

Age (yr)	Intelligence quotient	% nuclei with sex chromatin		Chromosome no	Maternal age (yr)
		Single	Double		
30	50	43	30	47	28
39	58	50	25	47	35
61	38	35	33	47	40+
73	50	33	30	47	

Buccal smears were stained by the original cresyl-echt-violet thod of Moore and Barr (1955), a hundred suitable nuclei ng examined in every case Mitotic chromosome counts re performed in 3 cases on cultures of peripheral blood by method of Hungerford et al (1959) with some modifications stly suggested by Miss Patricia Jacobs, and in 1 case on rnal marrow by the method of Ford et al (1958)

Results

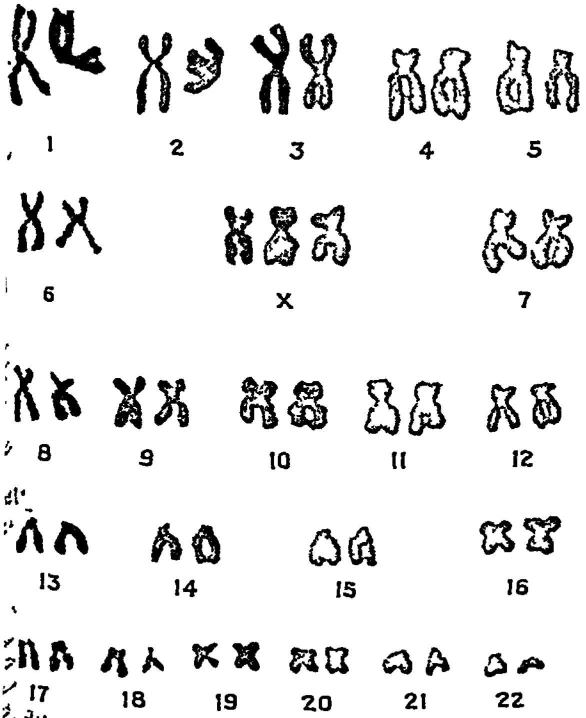
Of the 595 cases examined, 4 appear to be examples of XXX syndrome (see accompanying table) Buccal ears from all 4 show the characteristic high count of romatin-positive nuclei, many containing two sex-romatin bodies

In all 4 cases, chromosome counts showed a well-fined modal number of 47 In 3 cases preparations of fficient quality to permit detailed analysis were obtained, d in these it was readily established that the extra romosome is either an X, or at least something very near (see figure)

These 4 cases present no very striking clinical features, d they stand out in no characteristic fashion from the neral run of "non-specific" mental defect All 4 atients are blood-group A, and all are epileptics, but ese features may be coincidental Family studies have far disclosed nothing of note except high maternal age 2 cases

ertility

Disregarding the oldest patient, whose previous menstrual history cannot be obtained, all appear to have a normal or nearly normal menstrual history 1 of these patients, three years ago, gave birth to a single male child, and there is no doubt as to the maternity, as the child was born in the mother's present hospital The child appears to be physically normal and of average intelligence His mucosal smear is chromatin-negative, and blood-culture examinations show 46 normal chromosomes



gram showing 47 chromosomes and the 3 presumptive X hromosomes, identified as nearly as possible and numbered ccording to the "Denver" international system (1960)

Discussion

Our figures suggest that the frequency of the XXX syndrome among mental defectives is 0 7% It is improbable that the frequency of XXX in the general population will approach this figure The relatively high maternal age supports the view that non-disjunction is responsible for the chromosomal anomaly The figure is rather lower than that for Klinefelter's syndrome This may be a matter of chance, but it may be noted that, at least as far as non-disjunction at first meiosis is concerned, only maternal non-disjunction can give rise to an XXX zygote, so that one would expect the condition to be less common than XXY Klinefelter's syndrome

It is disappointing to find so far so little evidence of a characteristic syndrome In view of the normal menstrual histories, and the fertility of one of our cases, it is tempting to suggest that the extra X chromosome is producing no clinical effect at all, but it must at least be responsible for the mental deficiency

Our thanks to Mr N Russell for technical assistance, to Mr G Kerr for photography, and to Ciba Laboratories Ltd for a gift of 'Colcemid' alkaloid

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VENOUS THROMBOSIS DURING DEXTROSE INFUSION

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THROMBOSIS of veins during drip infusions depends on several factors The most important are prolonged infusion (Bolton Carter 1951), and chemical irritation from rubber tubing (Handfield-Jones and Lewis 1952) or dextrose solutions (Brian and Grainger 1950) The problem has been reviewed by Jones (1957) The effects of rubber tubing can now easily be avoided by using disposable plastic giving sets This makes it simpler to investigate the difficulties associated with the use of dextrose solutions

Dextrose solutions are usually sterilised in the autoclave This causes some hydrolysis, gluconic acid being formed (Hudson and Tarlowski 1947) Volksen (1952) has suggested that acid should be added to the solutions to preserve their colour Whatever the reasons, the solutions available commercially vary in pH from 3 5 to 4 5, and this acidity has been invoked as a cause of venous irritation and clotting Attempts have been made to counter the acidity by buffering the solutions (Bolton Carter et al 1952) Chemicals have been added to stabilise the dextrose during heating, or alternatively sterilising by filtration has been recommended (Brian and Grainger 1950)

The effect of acidity on thrombosis has been investigated Bolton Carter et al (1952) gained no benefit from buffering the solutions, but their test and control series were not concurrent Page et al (1952) found that buffering helped, but they used giving sets of various kinds, including rubber McNair and Dudley (1959) devised an ingeniously controlled trial in which thrombosis was not reduced by using filtered solutions, but they admit that the number of cases was too small to be conclusive

Aminoacid solutions are less irritant to veins when the pH is adjusted to 7 4 (Horvitz et al 1943), and it seemed to us that dextrose might behave similarly We therefore conducted a blind controlled trial of dextrose solutions sterilised by autoclaving or by filtration We found that autoclaved solutions are acid and that they are associated with a significantly higher incidence of thrombophlebitis than are filtered solutions whose pH is near neutrality We also attempted to answer several subsidiary questions, among them whether the use of giving sets for blood-transfusions before dextrose is infused increases the tendency to thrombosis Our results confirm previous observations on the association of length of infusion with incidence of thrombosis The final question of why acid-dextrose solutions cause venous thrombosis is still under investigation and will not be discussed further

Methods

The patients studied were admitted under the care of two surgical teams at the London Hospital Most patients underwent major gastrointestinal operations, but those with blood or biliary disorders were excluded Each was randomly allocated to receive either autoclaved or filtered dextrose solution at operation, and neither observers nor patients knew which was given

Plastic infusion sets only were used, and no other injections were given by this route The technique of setting up the infusions was standardised as much as possible, using either a needle or short cannula, without cutting down Signs of thrombophlebitis were recorded by the house-surgeon, using prearranged criteria Cases were classified as " trouble free ", " thrombophlebitis ", or " minor difficulties " " Minor difficulties " included all those which could not be definitely placed in the other groups They were mostly instances of the drip stopping without apparent cause or because of subcutaneous leakage Thrombophlebitis was diagnosed if a tender palpable cord or a red flare developed over the vein, in association with slowing or stoppage of the drip This was a simple working rule, but it tends to underestimate the true incidence of thrombophlebitis

The dextrose solutions were prepared in the same way, except that one was sterilised by filtration alone and the other was filtered and autoclaved The bottles were specially purchased, coming from the same batch of glass The rubber closures were all new, selected from the same batch, and subjected to the same preparatory techniques Anhydrous dextrose from one batch was dissolved to make a 50% solution in distilled water This was filtered through alkali-free (' Sterimat ' fibre) sterilising filter pads of SB grade into a sterile glass receiver The bottles, containing 150 m distilled water, were sterilised by heating in an autoclave cooling, 50 ml of the sterile 50% dextrose solution was to each bottle by an aseptic transferring device The res solution was the filtration-sterilised 5% dextrose solution in the trial The autoclave-sterilised solution was prepare adding 50 ml of the filtered 50% dextrose solution to 45 of distilled water in the giving bottle, and then autocla In this way any material extracted from the bottle glass, rubber closure, or the filter pad was common to both solu A similar technique was used to prepare 4% dextrose in 0 saline

TABLE I—THE RESULTS

Infusion	Thrombophlebitis	Minor difficulty	Trouble-free
Autoclaved	20	4	7
Filtered	9	6	13
Total no of infusions	29	10	20

Hæmolysis of stored citrated red cells by dextrose solu was investigated in vitro Measured volumes of stored b were allowed to stand in tubes of dextrose solution at r temperature These were centrifuged at intervals, and hæmoglobin in the solution was measured in a colorim using a green filter A microscopic check was made to en that the solutions had been centrifuged long enough red-cell envelopes to be removed

Results

Fifty-nine patients were included in the trial Ta gives the results according to the three categories alr defined

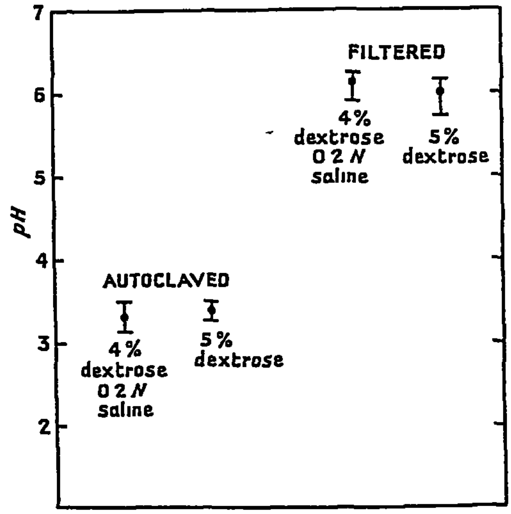
Because two teams were involved, and we suspected the previous use of the giving set for blood-transfusion m affect the results, the data were classified further b statistical analysis to show the effects of these factors (tabl The comparison between autoclaved and filtered solu shows that in each subgroup, thrombophlebitis was less quent with filtered solutions The difference between incidence with autoclaved and filtered solutions, and standard error, are shown in table II for each of the subgroups The weighted mean of these four differe (calculated by weighting each of the differences in in proportion to the square of its standard error) is 32% w standard error of 12%, which is significant at the 1% lev This shows clearly that thrombophlebitis is more comn with autoclaved than with filtered solutions

By a similar analysis the difference between the teams fails to be significant at the 5% level Tabl shows that for team A where the patient had ha previous transfusion of blood he was more likely to h thrombophlebitis after dextrose infusion, while for tea this was less likely This contrast between the two te is not significant, but it prompted a search for differen of technique It was found that team A used the sa giving set for glucose infusion after blood-transfus though it was rinsed quickly with normal saline Tea changed their giving sets but not the needles after bl

TABLE II—INCIDENCE OF THROMBOPHLEBITIS ACCORDING TO TYP DEXTROSE SOLUTION, TEAM, AND USE OF BLOOD

Infusion	Team A		Team B	
	Blood	No blood	Blood	No b
Autoclaved	11 15* (73 %)	5 7 (71 %)	1 3 (33 %)	3 7 (4
Filtered	5 11 (45 %)	2 8 (25 %)	0 2 (0)	2 7 (
Difference (autoclaved—filtered) (%)	34	46	33	14
± standard error	± 19	± 26	± 36	[illegible]

* No of infusions with thrombophlebitis total no of infusions



g 1—Means and ranges of pH measurements from groups of five bottles selected randomly from autoclaved and filtered solutions used in the trial.

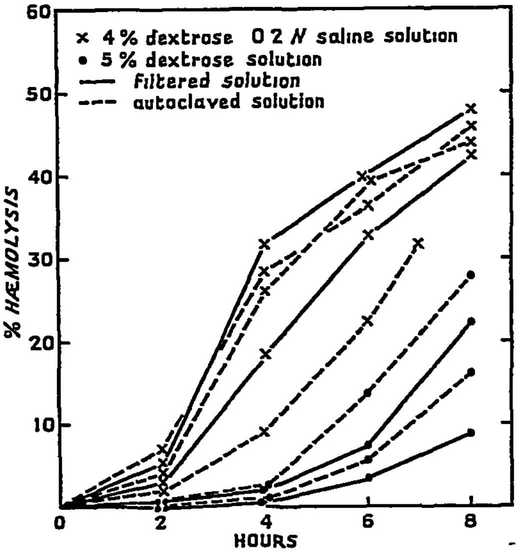
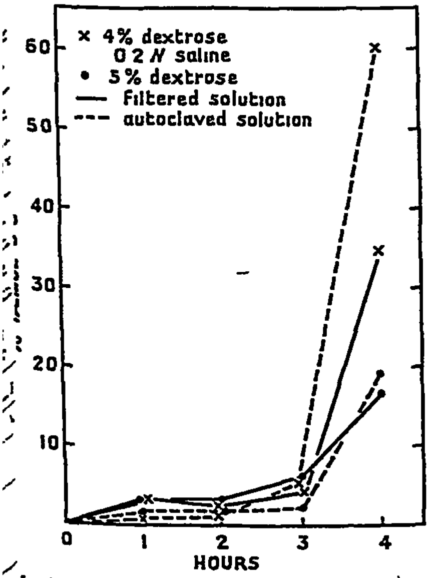


Fig 2—Hæmolysis of citrated red cells in various dextrose solutions at room temperature.

ad been given This difference had not been noticed uring the trial When blood had been transfused the iving-set filter carried much red-cell debris and other olid material, and when this was placed in dextrose olution the blood on the filter lysed The amount of lood was estimated, from the hæmoglobin released, to e about 5 ml

Five bottles were selected at random from each type of extrose solution used, the means and ranges of pH are hown in fig 1 for dextrose and dextrose-saline Investi-ation of the rate of hæmolysis of stored citrated blood in otonic dextrose solutions showed that 4% dextrose in ·2 *N* saline caused more rapid hæmolysis than 5% extrose The method of sterilisation (and hence pH) f the solutions had little effect (fig 2) During the rial the dextrose-saline solution was used after blood-ransfusion in nearly every case Fresh red cells (heparin-ed) showed a similar but more delayed pattern of æmolysis (fig 3)



ig 3—Lysis of fresh red cells in various dextrose solutions at room temperature

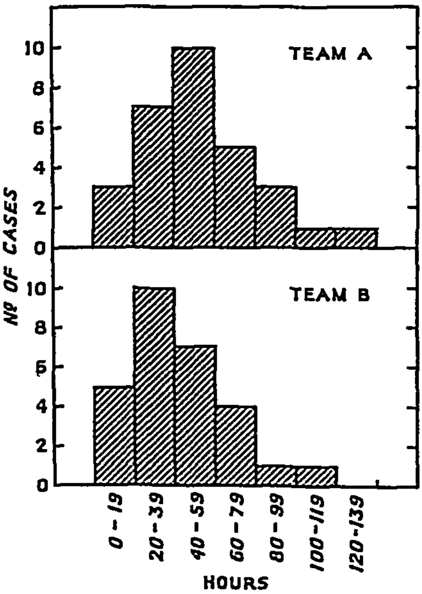


Fig 4—Length of infusions.

Team B had a lower incidence of thrombophlebitis both for autoclaved and filtered solutions (table II) This could be due to the shorter infusions (fig 4), although this difference was not significant

Discussion

Our results confirm the acidity of autoclaved dextrose solutions, and show that this was significantly associated with a high incidence of thrombophlebitis Commercial dextrose solutions are often more acid than the ones used in this investigation In one observer group the incidence of venous thrombosis reached 75%, but when filtered material was used it was only 36%

Transfusion of blood before glucose infusion was associated with more thrombophlebitis, but only in one observer group This was the group in which the same giving set was used for blood and dextrose solutions, and in which many patients must have received an infusion of broken-down red cells as already described This effect did not reach significance—perhaps because of the small numbers in the trial But the point seems worthy of further investigation since anything which favours red-cell breakdown is suspect as a cause of increased thrombosis

In-vitro investigation of hæmolysis of stored red cells by dextrose solutions showed that it was more frequent with glucose-saline solutions than with glucose alone, and it is interesting that glucose-saline was the solution commonly used after blood-transfusion The prevalence of hæmolysis following this procedure in children has been emphasised by Noble and Abbott (1959) Fresh red cells lyse in isotonic dextrose solutions after 3–4 hours at room temperature, but we have also observed that fresh blood in paraffin-lined tubes readily shows hæmolysis within 5 minutes when rotated gently at 37°C with isotonic acid-dextrose solutions This raises the possibility of hæmolysis in the vein used for infusion, but there is as yet no significant evidence of harmful effects from hæmolysis during dextrose infusion

Summary

When thrombophlebitis follows infusions of dextrose solution the irritant factor is now likely to be the solution itself

A controlled trial of acid and nearly neutral dextrose solutions (sterilised by autoclaving and filtration respectively) showed that thrombophlebitis is more than twice as common with the acid (autoclaved) solution

The infusion of dextrose-saline after blood-transfusion through the same giving set causes hæmolysis in the b retained in the filter, and these hæmolysed cells injected with the infusion

We are indebted to Mr W T Irvine and Mr J E R under whose care the patients were admitted, for help and en ment, and to Prof Clifford Wilson for much valuable crit thanks are particularly due to Mr R D Cohen, Mr J J F Ha and Mr G B Winter, who recorded the clinical obser without their meticulous help, together with that of many an ists and nurses, the trial would not have been possible

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New Inventions

A SUCTION TUBE FOR FREYER'S PROSTATECTOMY

SUCTION drainage for the Freyer's type of prostatectomy is often associated with leakage of urine and with introduction of infection The appliances usually employed require frequent attention and adjustment

The suction sump-drainage tube to be described has been used at Walton Hospital, Liverpool, and at other hospitals, on nearly 100 cases of Freyer's type prostatectomies over the past 3 years, and it has been found uniformly satisfactory

The suction tube is made of polyvinyl chloride throughout (fig 1) The outer tube, which corresponds in size to the Freyer's and Marion's tubes (30 HE size), is made in three lengths (marked on the tube)—i e, 5, 5½, and 6 in The inner (suction) tube is fixed by plastic "cement" inside the larger tube, with its lower end just above the level of the side hole, it emerges through the side of the outer tube at a point where a flap is made to support the bend of the inner tube The inner tube, which is 6 ft long, has an adaptor at the end for the suction apparatus The top of the outer tube is closed by a cuffed rubber bung which can be removed for the extraction of adherent clot from its lumen The air inlet is through the flap and a hole opposite

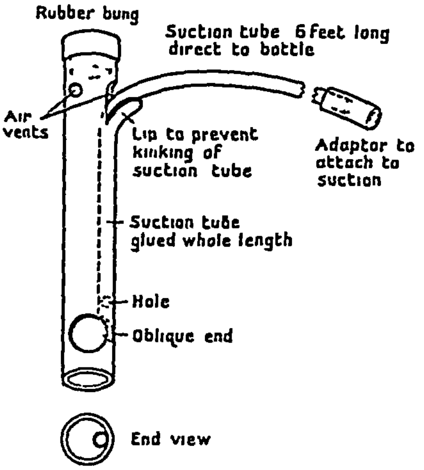
Rubber bung
Suction tube 6 feet long direct to bottle
Air vents
Lip to prevent kinking of suction tube
Adaptor to attach to suction
Suction tube glued whole length
Hole
Oblique end
End view

Fig 1

TECHNIQUE

The tube is sterilised by boiling, being coiled for this purpose and handled only by a ribbon

The length of tube selected (usually 5–5½ in) will to some extent depend on how obese the patient is The correct size will allow the suction tubing to lie almost flush with the abdominal wall (fig 2)

The prostate having been removed, and reasonable h stasis secured, the tube is inserted into the bladder in t usual way, and the bladder wall and wound are closed sn around the tube, which is fixed to the skin by a nylon st

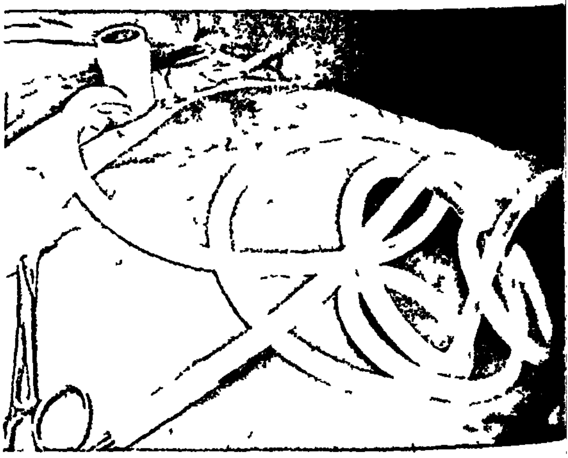

Fig 2

Suction is now started by means of the inner tube which attached to a Poole or Simpson-Smith sucker, this will de strate that the suction is working and prevent wound soil If any small clots have formed they can be washed o irrigating the suction tubing with saline or sodium-cit (4 3% solution)

The dressing, preferably of a few layers of gauze, is t placed over the wound and fixed by strapping The suc tube is strapped to the abdomen or upper thigh

As soon as the patient reaches the ward the suction tub is attached to a suction apparatus made by the Genito-Ur Manufacturing Co, which should have been previously chec This suction apparatus should keep the dressing dry, and t bladder free from introduced infection by avoiding rep inspection and adjustment

When the fluid sucked out is clear of blood, and the pati general condition allows, the tube is removed and the wo is firmly dressed A large Gibbon (size 9) or Foley (size 1 catheter is passed into the bladder per urethram

The apparatus can be used over and over again

The tube is made by Portex Plastics, Ltd, Bassett Ho, H Kent

My thanks are due to all the surgical staff at Walton H for their help, and also to Mr Jack Probert and Mr W Keogh, theatre technicians, who made all the prototyp skilfully

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MARTIN HO
[illegible] pool,

A STANDARD OBSTETRIC FORCEPS

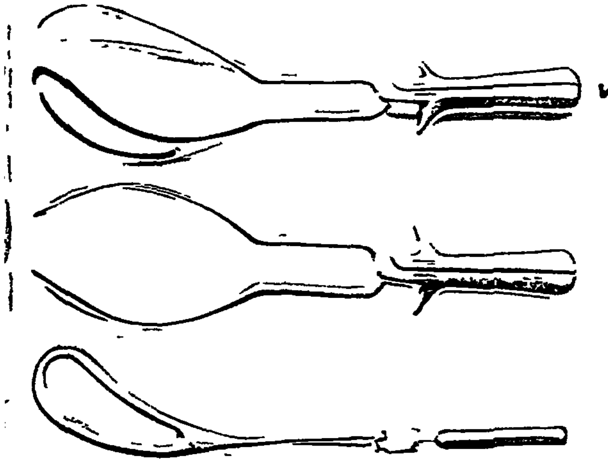
FORCEPS may vary in the important diameters which grip he fœtal head.[1] The variation is often seen between different atterns of forceps, but it may sometimes be seen in supposedly dentical forceps The reasons are that (*a*) different manuacturers have different standard patterns, (*b*) modifiers of re-existing forceps have often not laid down appropriate imensions, (*c*) fœtal head sizes may have increased in the past 00 years, (*d*) most forceps are still handmade, and (*e*) modern riters of textbooks do not agree on desirable dimensions of orceps

After measuring fœtal heads, and using Macdonald's igures[2] for fœtal-head size, theoretical dimensions for forceps or present-day practice were suggested These, which were ot regarded as final, were

istance apart of tips	3 0 cm.
idest distance apart of blades	9 0 cm.
ength of blade	16 0 cm.
adius of cephalic curve	11 25 cm.
adius of pelvic curve	17 5 cm.
ength of shanks	6 25 cm
idth apart of shanks	2 5 cm.

he length of the blade was measured in a straight line rom the tip to the beginning of the shank.

There is no difference of note between the construction of hese forceps and the general patterns in use, such as Simpon's, Ferguson's, Murray's, and Neville's (Kielland's forceps e standardised) But it was also decided to remove the [illegible] clutter of the past two centuries and so simplify forceps (see figure) In particular, the curve in the shanks of the Barnes-Neville forceps, and indentations in heavy handles, are no longer necessary Axis-traction devices have been discarded because the high forceps operation should not now be performed, this automatically does away with screws to hold the forceps together, and fishtail handles A similar simplified forceps, devised by De Lee, is figured in Greenhill's textbook.[3]



Allen & Hanbury's Ltd. (7 and 8, Vere Street, London, W 1) have made a pair of forceps to the above dimensions In use it was found that, because the widest diameter between the blades is slightly larger than that in most extant forceps, the tips of the blades bit into the baby's cheek and on one occasion caused a hæmatoma. The distance between the tip was therefore widened to 3 5 cm, and since that time they have caused no trouble in 18 months' continuous use at the Lambeth Hospital

The object of this communication is to draw attention to the variation in measurements of present-day obstetric forceps, and to lay down what seem to be reasonable standards for those who would like them

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1 Rhodes, P *J Obst et Gynæc Brit Emp* 1958, 65, 353
2 Macdonald, I Ibid 1953, 60, 61
3 Greenhill J P Obstetrics Philadelphia, 1955

Reviews of Books

An Atlas of Anatomy and Surgical Approaches in Orthopædic Surgery

Vol I Upper Extremity RUDOLFO CONSENTINO, M.D, assistant professor in orthopædic surgery, University of La Plata, Argentina Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 192 84*s*

IT is said that Abraham Colles, as a young boy, was playing in some deserted outhouses, when he came upon a discarded anatomical textbook. Its contents and vivid illustrations so fascinated him that thenceforth he could contemplate no other career than that of surgeon What would he have made of Dr Consentino's work? Here are none of the bold line drawings and multicoloured reticulations of most atlases The author has depicted human anatomy by photographing a series of dissections—not, of course, a new idea, but the limitations of even an expert photographer and a patient dissector are such that it has very seldom been a practicable one. Many atlases include a few photographs, but this one contains almost 150 pictures of the upper limb, including 20 illustrating the structure of the hand.

Everyone who looks at this book and who has wielded a camera or a scalpel will want to congratulate Dr Consentino on his results The text might, in places, be more happily phrased, and the black-and-white format lacks the appeal to move another youthful Colles, but place before an orthopædic surgeon, refreshing his memory about some structures he is to expose on the morrow, this book and the conventional polychrome and often rather fanciful atlas, and there is no doubt which he will choose.

✓Atrial Septal Defect

An Investigation into the Natural History of a Congenital Heart Disease H GOSTA DAVIDSEN, Rigshopitalet, Copenhagen Copenhagen Munksgaard 1960 Pp 225 D Kr 50

IN this book Dr Davidsen analyses postmortem reports of 190 cases of atrial septal defect which he has collected from the literature and describes 132 cases which he himself has studied clinically His aim is to determine the natural morbidity and mortality of this condition as a yardstick for the assessment of surgical treatment. Though he presents a great deal of information about the postmortem and the clinical series, he is largely frustrated in his intention, as he admits, by the diversity of the defect and its complicating anomalies, and by the impossibility, now that surgery is established, of finding an adequate series of untreated patients He has broken down his own series of 132 cases according to the anatomy of the defect, the presence of pulmonary hypertension, and the coexistence of other cardiovascular anomalies Even in this large initial series, many of these special groups are too small to yield significant results

The value of the analysis of the 190 necropsy cases is also doubtful Dr Davidsen admits that they are probably not typical of the condition as a whole, as is apparent from the high prevalence of associated anomalies—particularly lesions of the mitral and tricuspid valves Probably many were reported because they were unusual, and are not typical of the general run of cases

Though he has not achieved his main object, his extensive and thorough survey, and his selective and critical review of significant cases, will interest cardiologists -The figures are excellent, and the book can be recommended as a reference work.

The Divided Self

An existential study in sanity and madness R. D LAING, M B, D P.M, assistant physician, Tavistock Clinic, London London Tavistock Publications 1960 Pp 240 25*s*

THE first of a series of studies in existential psychology and psychiatry, this book is concerned with schizoid and schizophrenic persons, and its aim is to make madness and the process of going mad comprehensible. Looking at the schizophrenic from the standpoint of existential phenomenology is an attempt to reconstruct the patient's way of being himself in his world, and gives a very different picture from that obtained by the psychiatrist who is looking at the schizophrenic as someone "diseased" who shows various clinical symptoms As Dr Laing remarks, "The behaviour of the patient is to some extent a function of the behaviour of the psychiatrist in the same behavioural field The standard psychiatric patient is a function of the standard psychiatrist and of the standard mental hospital The figured base, as it were, which underscores all Bleuler's great description of schizophrenics is his remark that when all is said and done they were stranger to him than the birds in his garden"

Dr Laing postulates a need for the person to develop in early life a sense of ontological security, an abiding certainty of oneself as a person-for-oneself Lacking this, the individual feels unsure of his real existence and of the validity of his inner real self A "false self" is then developed, so that life can be carried on in apparent conformity with the outside world The complications that ensue from the split between the inner-self and the false-self system, both in the schizoid person and the frankly psychotic, are discussed and feelingly illustrated by the author's clinical observations of his patients They become beings less strange than Bleuler's birds as Dr Laing shows us round the garden Perhaps in another book we may learn about his relationship with these patients and his method of therapy that should make equally fascinating reading

Crash Injuries

JACOB KULOWSKI, M D, F A C S, F I C S, attending orthopædic surgeon, St Joseph's Hospital, St Joseph, Missouri Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 1080 260s

IN 1899 a passenger, alighting from a New York street-car, was struck by an automobile and received injuries from which he died the following day This was the first recorded motor-vehicle fatality in the United States, but a million and a quarter other deaths in that country have followed, and the total continues to rise at the rate of about a hundred a day These deaths result from violent forces applied over a very short period This book is a study of those forces, of the lesions they produce, and of the steps which can be taken to reduce them

About a third of the volume deals with the mechanics of road accidents and such matters as the stress tolerances of the human body, the remainder is concerned with their clinical aspect and the treatment of various types of injury

A great deal of interesting information is to be found in both sections There can be no argument about the value of safety belts, but there is still some doubt as to the best pattern Dr Kulowski, perhaps because he is greatly concerned about hip and pelvic injuries, favours the lap-strap design The driver who eschews a belt because he "never goes fast" should note that if his car hits a lamp standard at 30 m p h , he will be decelerated with a force which may exceed 170 *g* On the clinical side, mouth-to-mouth resuscitation is now advocated in preference to all other methods bv the American National Red Cross But no device has yet been found to supplant the Thomas splint for the first-aid treatment of fractures of the shaft and upper end of the femur

Portrait of Social Work

A Study of Social Services in a Northern Town BARBARA N RODGERS, JULIA DIXON London Oxford University Press (for the Nuffield Provincial Hospitals Trust) 1960 Pp 266 25s

THIS is a report, with commentary and recommendations, of a survey of the social work carried on in a northern industrial town of 100,000 inhabitants "with a great deal of local pride" The authors set out numerical facts clearly, but shun jargon and statistical tables, and they have written a lively, readable, cursive book with the emphasis on those who do the work—their deployment, training (or lack of character, outlook, and relation to their chiefs, work, other social workers, and social work in general.

Among those interviewed as likely to need help from s workers or to know of their work, general practitioners only a sketchy knowledge of the scope of social work almost no direct contact with social workers even in the h services The authors' first plea is for making the princ and aims of social work more explicit They believe that more social workers should have a recognised training, bo improve their efficiency and, still more, to give them a fessional outlook on themselves, their work, and colleagues and professional status in the eyes of those employ them or come in contact with them Only the Gov ment, the authors consider, can initiate the necessary refo

Ovum Humanum

LANDRUM B SHETTLES, M D, PH D, assistant profess clinical obstetrics and gynæcology, College of Physicians Surgeons, Columbia University New York and Lo Hafner Publishing Company 1960 Pp 79 55s

IN this book Dr Shettles seeks to fill the gap in the stud human embryology due to the paucity of direct observat on the human ovum during its growth, maturation, fertil tion, and the week of its preimplantation life He has achi his end by presenting a beautiful pictorial record of the hu ovum's development during these early stages The leg to the figures are in German, French, and English.

Essays and Studies, 1960

Collected by M ST CLARE BYRNE Volume XIII of the series collected for the English Association London J Murray 1960 Pp 114 13s 6*d*

THOSE who regard litigation between doctors and patie or their relatives, as a relatively modern phenomenon will interested in Prof C J Sisson's description of a legal actio which William Harvey was involved In 1620 Harvey was of a number of physicians asked to examine a wealthy m Sir William Smith, afflicted with symptoms attributed t stone The other consultants urged that lithotomy be p formed, but Harvey counselled conservative treatment, and use of his own secret remedy Within a few months (and a rejecting Harvey's advice, and undergoing an operation) patient died His executors refused to meet the doctor's and the matter went to Chancery where Harvey eventu won his suit A detailed account of the case is to be found the first article in this book, the latest in a series of liter studies published for the English Association

The Population Explosion and Christian Responsibil

RICHARD M FAGLEY New York and London Oxford Un sity Press 1960 Pp 260 28s

THIS book, by a minister of Congregational Churc U S A, with special experience of international proble purposes to bring home to readers, especially Christians of Western Protestant churches, the menace of the sudd violent, and progressive increase of world population, to wh the word "explosion" quite accurately applies Christia Dr Fagley urges, should, as a matter of great urgency, face facts, frame an agreed policy, particularly on birth cont and press reluctant Governments and international bodies take what action they can to stem the increase by means ot than abortion, infanticide, famine, or war Erudition, schol ship, and moderation pervade the book, every statemen authenticated and each quotation has its reference

Medical readers may not feel like tackling the more th logical chapters, good though they are, but medicine is no responsible for the population explosion than is physical scie for the atom bomb, and technical aids to controlling it m flow largely from medicine The problem is therefore v definitely of concern to the profession, and any who doubt reality or gravity or believe in easy remedies should at le read Dr Fagley's first six chapters

THE LANCET

LONDON 17 SEPTEMBER 1960

Future Maternity Hospitals

THERE is every indication that in the second decade of e National Health Service capital expenditure will be bstantially increased New hospitals will be built and d ones replaced But the allocation of priorities will t be easy, for there has been no serious study of e country's overall need for hospital beds[1-3] The uation in regard to maternity is probably clearer than ost, for, however the number of beds needed for tients of certain ages or with certain diseases may wax wane, women will certainly continue to have babies, d the demand for hospital confinement has risen eadily in the past twenty-five years

Many of today's maternity hospitals have been conrted from older buildings, or have developed pieceeal as the obstetric service, particularly the antenatal ction, has evolved This has led to some rigidity in sign, with clear separation of antenatal and postnatal ards and usually a central delivery suite Continuity of rsing and medical care is difficult, if not impossible, nder these circumstances STABLER[4] has suggested at the future maternity hospital should be built around series of self-contained units of 10–15 beds, each with s own delivery room, but that a central operatingeatre should be retained Throughout her pregnancy e patient would remain under the care of a small roup of nurses and doctors attached to one of the units, nd patients suspected of being infectious would be ursed on these units rather than in a separate isolation ard This plan, though attractive in many ways, equires further study The idea of nursing possibly fectious cases on the small units is unlikely to find uch support Mothers with undiagnosed infections re a source of anxiety and danger tuberculosis and ysentery are two examples of maternal infections which ay hazard the lives of newborn infants A small isolaion ward is still needed in any maternity hospital

The issue of central or dispersed labour wards is rucial Here there are two important considerations irst, close supervision by experienced midwives is ssential in the labour ward Owing to shorter working ours and arrangements for off-time and night duty, it is lready difficult to maintain the necessary standard even n a central delivery suite Dispersal is bound to raise resh nursing problems Secondly, unexpected comlications may arise in labour and necessitate the atient's immediate transfer to the operating-theatre Movement of a patient, particularly under an anæsthetic, from one part of the hospital to another is dangerous corridors may be crowded at visiting-time, and the best of lifts may break down On balance a central delivery suite next to the theatre is likely to be safer and more efficient Possibly the architect, aware of these circumstances, can design small ward units in such a way that their delivery rooms are immediately adjacent to the operating-theatre In this event the delivery rooms could be staffed by nurses either from the ward units or from the central operating-theatre Experience would show which of the two arrangements is preferable

At present babies are customarily nursed in cots by their mothers' beds, but each ward must have a small separate nursery with 2 or 3 cots for noisy babies at night and for other babies who require temporary cot-nursing apart from their mothers The Central Health Services Council[5] has suggested that in each region special units for the care of premature and other abnormal babies should be restricted to a few of the larger maternity departments which cater for abnormal obstetrics This is a realistic approach, for the necessary standard of nursing and pædiatric supervision cannot be maintained in small special nurseries scattered throughout the region The Council suggest, too, that each special baby-care unit should have at least 20 cots—enough for a population of 200,000 These larger hospitals with special baby-care nurseries would accept women in premature labour and premature and other abnormal babies from other maternity hospitals and from domiciliary practice

The small isolated maternity hospital is at an increasing disadvantage Unexpected developments in pregnancy or labour may call for immediate attention not only by obstetrician and pædiatrician but also by physician, hæmatologist, blood-transfusion officer, biochemist, radiologist, anæsthetist, and others Modern obstetric practice demands that maternity hospitals be sited immediately adjacent to general hospitals where these special skills are at hand In his second Ingleby lecture, which we publish this week, Sir DUGALD BAIRD speaks of the great advantage, to a regional maternity service, of having a teaching hospital as its central point and a really close association with the public-health department These are among many things he describes whose value, in everyday life, has been proved in Aberdeen

Future hospital plans should take into account the need for general-practitioner beds, and this will involve administrative as well as planning difficulties Many general practitioners oppose the recommendation of the Cranbrook Committee[6] that their beds should be under the general supervision of the consultant staff, and would opt for a separate autonomous unit close to the hospital Such an arrangement would perpetuate the fragmentation of the maternity service Much preferable would be a general-practitioner unit within the framework of the hospital, in which family doctors would accept the

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Times June 16 and 17 1960

[2] The Demand for Medical Care. Nuffield Provincial Hospital Trust. London 1960

[3] Creative Leadership in a State Service. The Acton Society Trust. London 1959

[4] Stabler, F E. *Lancet*, 1959, i 299

[5] Report of the Central Health Services Council for the year ended Dec. 31, 1959 H M. Stationery Office 1960 See *Lancet* July 9 1960, p 92

[6] Report of the Maternity Services Committee. H.M. Stationery Office, 1959 See *Lancet*, 1959, i, 397

clinical discipline of the hospital as do all members of staff, including the consultants

In its report the Cranbrook Committee set out the arguments for and against a unified maternity service based on the hospitals Although the committee decided that this was not the time to alter the tripartite structure of the service, it clearly foresaw that spontaneous cooperation could lead eventually to integration and a unified service in which hospital and domiciliary practice would be complementary Certain hospitals already have a satisfactory arrangement with their local medical officer of health whereby domiciliary midwives, during the antenatal period, visit selected patients who are booked for hospital delivery and take over nursing supervision when the patients are discharged forty-eight hours after delivery[7] An interchange of hospital and domiciliary midwives, also contemplated by the Cranbrook Committee, would be a natural development of the early-discharge scheme On the one hand this would give the hospital a more intimate link with the community it serves, and on the other it would provide the domiciliary midwife with greater opportunities for keeping abreast of advances in obstetric practice This may be the future pattern of maternity care in the country, and it could be achieved with little or no increase in the number of hospital beds

So far as maternity is concerned, any available capital might best be spent on replacing and re-siting the older hospitals Today's patients are increasingly aware of the old-fashioned appearance of wards in which bathrooms are too few and privacy is lacking, of the failure to provide day-rooms where they can read or write in peace, and of the air of austerity which pervades the hospital[8] Improvement in hospital design should be matched by a more sympathetic understanding of the mother's emotional needs[9] A heavy responsibility rests on the shoulders of the senior medical and nursing staffs, for they, by their example and teaching, largely determine standard and the atmosphere throughout the hospital

Anæsthesia for Neurosurgery

GREAT strides have been made in anæsthesia for neurosurgery, but the improvements have mostly resulted not so much from new physiological and pharmacological knowledge as from empirical application of established techniques Our knowledge of the effects of drugs and techniques used in anæsthesia on that most vital factor—the bulk of the brain—remains hopelessly incomplete and confused It was long believed that change in the cerebral blood-flow was the main determining factor drugs which produced cerebral vasodilatation would increase the local blood-flow and thus the brain bulk, and so would agents which depressed respiration, since the accumulating carbon dioxide would exert a similar influence Yet agents which are known to have these undesirable properties have been regularly recommended for neurosurgical Thus WYLIE[1] some years ago reported excellent r with pethidine as a supplement to nitrous oxide oxygen, even though pethidine undoubtedly depre respiration and presumably promotes retention of car dioxide The position as regards the lipoid-solubl plements to nitrous oxide and oxygen is eq unsatisfactory Trichloroethylene was long the agent for this purpose in neurosurgical work[2,3] is well known to have vasodilator properties and reduce the tidal volume in the presence of tachyp The position with halothane is even more ludicro for this substance has far greater vasodilator act than trichloroethylene and is beyond doubt a respira depressant, and yet despite these apparently undesir properties many anæsthetists have found it to b most satisfactory agent for neurosurgical anæsthesi

The wide acceptance of controlled respiration certain types of neurosurgical anæsthesia is ano indication of the present confusion, for the physio basis for its use is obscure Besides cerebral blood- the other main factor determining the pressure in cranium is usually believed to be the pressure the veins there, and this is said to be the pressure in great vessels of the thorax minus the height of the above the mediastinum Controlled respiration raise the pressure in the chest, for it substitutes for normal recurring inspiratory increase in the in thoracic negative pressure a rhythmic positive press which is transmitted in part to the mediastinum no doubt to the vessels there According to cur theory, therefore, it will also raise the pressure in cranial cavity Some anæsthetists, indeed, believe something of this sort happens and regard a respir with a negative phase as essential[6] HUNTER,[7] howe has indicated that the pressure swings produced b respirator in the mediastinum are not accompanied comparable changes in the intracranial pressure, he has suggested that the veins in the neck, which well known to fill and empty during normal respirat act as a sort of reservoir in which changes in press are converted into changes in volume, with the re that the intracranial pressure remains largely [illegible] by the modification in the breathing inherent in artifi ventilation of the lungs

Apart from these basic considerations the success controlled respiration in neurosurgery raises an import practical issue For years surgeons and anæsthet alike have used changes in the rate and character respiration as a guide to the state of certain vital ar of the nervous system In the paralysed and artifici ventilated patient, however, the surgeon can (at least theory) invade those parts of the brain concerned maintaining respiration without his receiving any wa ing of the trespass this risk is perhaps greatest dur oval of a large tumour in the posterior fossa Sur- n and anæsthetist have to weigh the advantages and backs of controlled respiration against those of the r methods of reducing the intracranial pressure, as the sitting position, the administration of urea,[8] ganglionic blockade[9] It must not be assumed that ngle technique will be satisfactory in all cases An sthetic method which proves highly satisfactory for tient with a pituitary tumour operated on in the ne position may be anything but satisfactory for a ent who has a posterior-fossa tumour removed in sitting position. Perhaps we have tended to think much in terms of anæsthesia for neurosurgery rather n of the anæsthetic technique appropriate for each the many different operations undertaken by rosurgeons

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[7] City and County of Newcastle upon Tyne Annual Report of the Medical Officer of Health 1959

[8] See *Times* March 23 1960

[9] See [illegible] *Lancet* 1960 i 913

[1] Wylie W D *G[illegible] Anest* 1951 17 1

[2] Ballantine, R I W *Anæsthesia* 1956, 11, 303

[3] McBurrows M Dundee J W, Francis, I L Lipton S, Sed C B *ibid* p 4

[4] Brindle G F, Gilbert R G B, Millar, R A *Canad anæsth S* 1957 4 265

[5] Campkin V Inglis, J M *Brit J Anæsth* 1959, 30, 506

[6] Galloon S *Anæsthesia*, 1959 14, 223

[7] Hunter, A R *Proc R Soc Med* 1960, 53, 365

Drug Treatment of Alcoholism

ow useful are drugs in the treatment of alcoholism ? he withdrawal phase the main aims are correction of ydration and malnutrition, and sedation. Vitamins ecially the B complex) are given in high dosage, at t parenterally and later orally (vitamin injections are required in the treatment of certain complications, h as peripheral neuritis, Korsakow's psychosis, and rnicke's encephalopathy) To calm the tense, ious, agitated, and restless alcoholic, tranquillisers now usually given, by injection or orally Chlor- omazine,[10] promazine,[11] trifluoperazine,[12] other pheno- azines, and meprobamate[13] have all proved of value e tranquillisers are at present the drugs most nmonly used in the management of delirium tremens, hough the old standby, paraldehyde, is still favoured some. A few years ago, especially in the U S A, renal cortical extract and corticotrophin were often ployed in the treatment of delirium tremens, t controlled experiments failed to show that " the ults were superior to those obtained with lation, vitamins and other supportive measures "[14] anquillisers may also decrease the risk of withdrawal mptoms, though these are now rare[15,16] even after dden complete withdrawal of alcohol Phenytoin may o be given in order to prevent convulsions in this ase

In the acute alcoholic stage sleeplessness is often oublesome, and hypnotics may be necessary Many oholics are prone to use to excess any sedative or imulating drug[17]—in particular the barbiturates and raldehyde, but also meprobamate, amphetamines, and enmetrazine On the whole, therefore, non-barbiturate pnotics, such as thalidomide, methpyrlone, and utethimide, are preferable, though even these are not e from the risks of habit-formation and addiction[18]

Administration of disulfiram is usually restricted to long-term treatment, but Martensen-Larsen,[19] who was the first to administer this drug to alcoholic patients, also recommended it (in combination with the anti-histamine promethazine and sodium chloride) as the treatment of choice for intoxication

The tranquillisers are sometimes used also in the long-term management of alcoholism for purposes such as helping the " dry " alcoholic over periods of anxiety and tension and encouraging him to keep in regular touch with the therapist. Undue dependence of alcoholics on any drug, however, should be avoided Only three of the many substances recommended in the past as aiding the alcoholic to maintain sobriety are now in more or less widespread use Probably the most popular is disulfiram[19] This inhibits the breakdown of alcohol at the acetaldehyde stage Thus if, having taken disulfiram, the patient consumes alcohol within the next three days or so, he may experience extremely unpleasant or even life-threatening symptoms The knowledge of the risks involved (or the experience of a disulfiram-alcohol test carried out in hospital) is in most cases enough to deter the patient from drinking so long as he continues to take the tablets The minimal maintenance dose varies from case to case. Special caution is needed in the presence of such conditions as heart-disease or liver cirrhosis, and on no account must the drug be given without the patient's knowledge (there have been instances where the tablets have been added to the alcoholic's tea by his desperate wife) Many have found disulfiram an excellent adjunct even though for the alcoholic it is often easier to give up taking the tablets than the alcohol But then no treatment can be expected to succeed unless some motivation to stay sober is present from the start or is induced by psychotherapy

In recent years another substance, citrated calcium carbimide (C C C)[20] has been used with the same aim as disulfiram. Sensitisation to alcohol occurs sooner with C.C C than with disulfiram, the alcohol reaction and the side-effects are milder, and the " protection " afforded does not last so long[21,22]

Emetine is another drug often used in alcoholism The aim here is to produce an aversion against the sight, smell, and taste of alcohol. On a series of occasions, separated by rest periods, the drug is injected and shortly afterwards alcohol is drunk, so that in time a conditioned reflex is established[23,24] Finally, apomorphine is sometimes injected to induce aversion, as with emetine. But Dent,[25] the main advocate of apomorphine treatment in this country, strongly disagrees with this view and maintains that the drug works mainly by allaying anxiety and craving Dent has also devised a simple method of giving apomorphine by mouth (without subsequent administration of alcohol) to outpatients and in general practice

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8 Stubbs, J Pennybacker, J *Lancet* 1960 i 1094
9 Hewer A J H *Proc R Soc Med* 1952 45 431
0 Feldman D J *Med Clin N Amer* 1957 41 381
1 Browne L W, Ryan J P A, McGrath, S D *Lancet*, 1959 i 959
2 Cohen S Ditman K S, Mooney, H B *in* Trifluoperazine (edited by H Brill) Philadelphia, 1958
3 Sargant, W *Brit med J* 1958, ii 1095
4 Berman, L H *Quart J Stud Alc* 1956, 17, 25
5 *Wld Hlth Org tech Rep Ser* 1955, 94 7
6 Glatt, M M *Brit med J* 1955 ii, 738
7 Glatt, M M *ibid* 1958, ii 1100
8 Glatt, M M *ibid* 1959, i, 50

19 Martensen-Larsen O *Quart J Stud Alc* 1953 14, 406
20 Ferguson J K W *Canad med Ass J* 1956, 74, 793
21 Armstrong J D *ibid* 77, 228
22 Glatt M M *J ment Sci* 1959, 105, 476
23 Voegtlin, W L, Lemere, F *Amer J med Sci* 1940, 199, 802
24 Williams, L Alcoholism Edinburgh 1956
25 Dent, J Y Anxiety and its Treatment London, 1955

No one form of therapy will produce the best results in every alcoholic.[26,27] Individual assessment should be followed by a combination of psychological, physical, and social techniques, and the contribution which Alcoholics Anonymous can make should not be forgotten. The doctor's attitude to the patient may be more important than the drug he prescribes. The training of medical students in the treatment of alcoholism is often sadly deficient, but, even so, there is little excuse for pretending that this disorder can be treated by dispensing moral exhortations and barbiturate tablets.

Annotations

SHORTAGE OF DIETITIANS

A DIETITIAN is needed in a general hospital if patients are to benefit from present-day knowledge of nutrition. The role of dietitians may have become less prominent in the management of peptic ulcer, but careful dietary control is needed in some illnesses—particularly heart-failure and hepatic disease. The dietitian greatly facilitates the work of the diabetic clinic, and she has useful work to do in advising pregnant women and mothers of young children on correct feeding. Moreover, she can make a real contribution as a nutritionist by working with the catering officer and by lecturing to the nurses on proper feeding in health and disease.

King Edward's Hospital Fund for London has recently published a memorandum on the Shortage of Dietitians[28] based on discussions held with interested parties including doctors, dietitians, the Ministry of Health, and the Royal College of Nursing. Concurrently an investigation was undertaken jointly by the Fund and the Ministry of Health into the present work of dietitians in the hospital service, and this is reported in part II of the memorandum.

Unfortunately only a few hospitals today can provide a full dietetic service, and the increasing shortage of dietitians has now become very apparent. A survey of the fourteen hospital regions of England and Wales showed that there were only 95 therapeutic dietitians or caterer dietitians. There is, however, a greater concentration in provincial and London teaching hospitals, where 112 were employed. Fortunately, despite the shortage of dietitians the subject is not entirely neglected, as interested ward sisters and catering officers often make a substantial contribution to dietetics in a hospital, but beyond doubt a great many patients in British hospitals are not getting the full benefit of modern nutritional knowledge.

Several factors have contributed to the present shortage of dietitians. An important one is the length of training. There are two avenues. For the first a preliminary qualification, consisting of one of the following, is needed: a degree in pure science, household science, or nutrition, a domestic science teacher's diploma, an institutional management diploma, a specified catering diploma, or training or State registration in nursing; and this is followed by a dietetic diploma course of 15–18 months. Alternatively, there is a dietetic course of 3 years' duration. It is now widely felt that what is needed properly integrated course of training lasting 3 y or perhaps even less. Furthermore the salary scales been unsatisfactory, and there has been a substantial from the hospital service into the school meals servic industry. A salary scale based only on the numbe assistants is never satisfactory, and this arrangement have helped to bring about the excessive concentratio dietitians in relatively few hospitals. Medical staffs accept some responsibility for the present difficulties, their interest or indifference makes a great difference to success of the dietetic department.

The modern dietitian has much more to offer the supply of a few weighed diets, and, if allowed to, can make a very valuable contribution in the outpa department and on hospital nutrition in general hospital which does not enable the dietitian to take meals with the ward sisters cannot expect to retain services of an intelligent, well-trained person. The much to be said for the medical staff committee nom ing one of its members to help a new dietitian in coordi ing her work and in dealing with the initial administra problems.

PORPHYRIA IN IRELAND

THE least common of the porphyria group of di is congenital porphyria, yet the first recorded ca porphyria, reported in 1874,[1] was undoubtedly of type. Since then only 18 such cases have been de Apart from sunlight, non-genetic factors are unimpo in precipitating the symptoms of congenital porph On the other hand, in acute intermittent porph though the disorder often develops spontaneously, cipitating factors, especially drugs, are important 1889—a year after the introduction of sulphon Stokvis[2] reported a case of acute porphyria in an el woman who had taken this drug, and other such re followed. The introduction of barbiturates in 1903 le a similar crop of cases of acute porphyria.

Studies of acute porphyria, and to a lesser exte porphyria cutanea tarda,[3] have revealed an appa increase in their prevalence. A striking fact is tha both Sweden and Australia the prevalence of a porphyria is about 1·5 cases per 100,000, wherea Northern Lapland and in South Africa the figure is higher—1 per 1000 and 1 per 100 respectively—bec in each of these regions an early prolific ancestor ca the genetic trait.[3]

Fennelly et al.[4] find that up to 1950 no case of porph had been described in Eire, but they now list 50 rep cases, including fourteen families with acute porp and one with porphyria cutanea tarda. This giv prevalence in Eire of 1 in 80,000 of the total popula which is about the same as in Australia and Sw The prevalence in Northern Ireland may be high possibly 1 in 5000, according to Stevenson.[5] These fig include latent cases of acute porphyria and of porp cutanea tarda—that is, subjects with the genetic who excrete porphobilinogen or porphyrins respecti but who have no symptoms. The clinical picture of t diseases in Eire differs in no way from that of

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[26] Wallerstein, R. S., Chotlos, J. W., Friend, M. B., Hammersley, D. W., Perkins, E. A., Winship, G. M. Hospital Treatment of Alcoholism. London, 1957.

[27] Glatt, M. M. Lancet, 1955, i, 1318.

[28] Memorandum on the Shortage of Dietitians. Pp. 38. 2s. Obtainable from King Edward's Hospital Fund for London, 34 King Street, London, E.C.2.

[1] Schultz, J. H. Ein Fall von Pemphigus leprosus, kompliziert durch visceralis. Greifswald, 1874.

[2] Stokvis, B. J. Ned. Tijdschr. Geneesk. 1889, 2, 409.

[3] Lancet, 1959, ii, 93.

[4] Fennelly, J. J., Fitzgerald, O., Hingerty, D. J. Irish J. med. Sc p. 130.

[5] Stevenson, A. C. Radiation Res. 1959, 1, suppl. 1, p. 306.

hyria[5, 6] and porphyria cutanea tarda[6, 7] in England and land Fennelly et al stress the dangers of barbiturates, cially barbiturate anæsthetics, but agree with Gold- [5, 6] that only in those with the genetic trait may an e attack be precipitated by barbiturates

ny notable increase in the prevalence of the genetic , as in South Africa, will require many generations, the introduction of a widely used drug which adversely cts porphyrin metabolism might significantly change incidence of the active disease For this reason, those ting porphyria families should be particularly circum- t in administering any new drug

MUSCLES OF RESPIRATION AND SPEECH

r is generally assumed that the intercostal muscles as l as the diaphragm take part in normal quiet respira- and that expiration is passive Clinical experience ws that respiration can be maintained without active phragmatic movements From the way in which the rcostal muscles are attached to the ribs it was believed the external intercostals raise the ribs and increase diameter of the thoracic cavity, and so act as inspiratory scles, and that the internal intercostals are used only igorous expiration or to maintain the distance between ividual ribs These same muscles, and others, must be concerned in the precise regulation of expiration essary in speaking and such occupations as playing d instruments

btaining direct information about each muscle calls ingenuity and skill on the part of the investigator a certain hardihood on the part of the subject The t direct proof that an unseen muscle is contracting is appearance of action potentials recorded from leads ached to electrodes inserted in the muscle The ficulty about applying this technique to the inter- tals is that they form two thin closely contiguous ets of muscle whose movements are such that the ets tend to slide in opposite directions, but there are as where one or other muscular sheet is deficient and remaining one can be observed without difficulty e diaphragm forms a dome over the abdominal viscera, d when needle electrodes are inserted into it care must taken to avoid the viscera and pleural cavity

An ingenious way of circumventing this difficulty is the subject to swallow the electrodes till they come to at the plane where the œsophagus passes between e diaphragmatic crura[8, 9] Accurate information about tratracheal pressures can be obtained by passing a small lloon and tube through the nose till the former lies hind the posterior soft part of the trachea just above e bifurcation Check experiments have shown that ese techniques give reliable information When air is st only slowly through the mouth, then mouth pressure flects intratracheal pressure For wind-instrument ayers a manometer can be used, connected to a small be which passes through the corner of the mouth and es not disturb lip work[9, 10]

Finally all these measurements have to be correlated ith the phase of respiration Where speech is to be udied, obviously any form of spirometer or pneumo- chograph is out of the question Instead the subject n be inserted up to the neck in a large plethysmograph which records the air displaced from the tank during respiration[8, 9] By combinations of these techniques it has been found that in quiet breathing the diaphragm is almost wholly responsible for inspiration, and that action potentials appear in it before the inward flow of air begins[11] Apparently the external intercostals are not used in quiet inspiration, but an upper part of the internal intercostals, where the muscles are not covered by the external layer, is used A lower part of the internal intercostals contracts during expiration In addition, diaphragmatic activity does not cease until some time after expiration has begun[11] Thus quiet expiration is not, as was formerly thought, a wholly passive process In forceful breathing both external and internal intercostals are used and the transversus thoracis aids in expiration,[11] as well as all the large accessory muscles such as latissimus dorsi, rectus abdominis, and external oblique

For speech, air has to be expired in regulated bursts in order to make the various sounds, and each expiration must last long enough to give meaning to phrases Singing and the playing of wind instruments demand even finer control of rate of air-flow and pressure of supply in order to regulate the volume and quality of sound produced In quiet talking tracheal pressure is of the order of 2 cm water, and a parade-ground shout raises this to between 20 and 30 cm water[9] If loudness is kept constant tracheal pressure must also be maintained, despite a steadily decreasing volume of air in the lungs The necessary pressure is produced by the thoracic muscles which oppose the natural elastic recoil, or compliance, of the lungs and chest wall At the beginning of speech with full lungs, the external intercostals hold the thorax in a slowly declining " open position ", then their activity decreases unit by unit, and overlaps with the onset of activity in the internal intercostals which slowly compress the lungs in order to maintain the required steady pressure As the lungs empty still further, other muscles are brought in to help keep up the pressure—for example, latissimus dorsi and, at the end of a long phrase, rectus abdominis[8, 9] The louder the utterance the earlier the expiratory muscles must begin to contract Apparently, in most people during speech the diaphragm shows little activity and expiratory control depends on coordination between the external and internal intercostals The object throughout is to regulate pressure below the vocal cords Paraplegics use any available muscle—commonly, for example, latissimus dorsi With a high spinal injury adduction of the scapulæ can be used[9]

The pitch of a voice depends on the tension in the vocal cords, and this is adjusted by means of the intrinsic laryngeal muscles before any audible sound emerges The controlled intratracheal pressure forces air past the glottis, and separates the margins of the cords setting up a series of vibrations and recoils These facts were ascertained by inserting fine needles in the laryngeal muscles and recording the action potentials[12]

The internal intercostals seem to be used a great deal in making fine pressure adjustments in speech and enabling stresses to be made They go into activity measurably before speech begins and can fluctuate almost as rapidly as the small muscles of the hand[8, 9] Other respiratory muscles do not show the same rapid variation in activity In some subjects the external intercostals exert a check action after a stressed syllable and thus momentarily oppose the outward air flow induced by the

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Goldberg A *Quart J Med* 1959 28, 183

Holti, G Rimington, C, Tate B C, Thomas G *ibid* 1958, 27 1

Draper M H, Ladefoged, P, Whitteridge, D *J Speech Hearing Res* 1959, 2, 16.

Draper, M H., Ladefoged, P, Whitteridge, D *Brit med J* 1960, i, 1837

Faulkner, M, Sharpey-Schafer, E. P *ibid* 1959, i, 685

[11] Taylor, A *J Physiol* 1960, 151, 390

[12] Buchthal, F *Quart J exp Physiol* 1959, 44, 137

internal intercostals At a fairly regular interval after internal intercostal activity begins, tracheal pressure increases and then sound follows

A skilled player of a wind instrument uses the same muscles as a singer or a speaker, but far more often he has to produce a large volume of sound—that is, a high intratracheal pressure An expert trumpet player on a loud top note produces an intratracheal pressure of 80 mm Hg, or even occasionally 160 mm Hg, the oboe often demands 60 mm Hg, the clarinet and French horn somewhat less, and the flute least of all [9,12] In fact, the problem with the flute is to maintain long phrases at a low pressure, in contrast with the trumpet, which may need long phrases at high pressure When playing the trumpet, as may be imagined, considerable circulatory changes are inevitable and dizziness or blackout can occur from the equivalent of the Valsalva manœuvre [12] Yet these pressures are nothing compared with those produced by a violent cough in a muscular subject, when the intratracheal pressure may be as high as 200–450 mm Hg [13]

ADDER-BITES AS A HOLIDAY HAZARD

ADDER-BITES are becoming commoner in the south of England as a result of the influx of holidaymakers The increase is attributable partly to the tent, caravan, or bed-and-breakfast, with its compulsory outdoor meals and lack of sanitation the holiday season from July to mid-September coincides with the breeding season of *Vipera berus* Adders are extremely local in their habitat, some country practitioners in Cornwall have never seen a case of adder-bite in thirty years' practice, while one not ten miles away treats at least 3 a year In a review of the past eight years in Cornwall, Morton [1] has reported 18 cases All the bites were on the extremities, and of 12 cases seen by him personally only 4 were accidental, the other 8 followed attempts to capture the snake under the impression that it was a harmless grass snake

The only death associated with snake-bite in England in the last nineteen years was attributed to cardiovascular collapse from anaphylaxis due to the serum given a few minutes earlier [2] The venom of *Vipera berus* is not very toxic for a 600 g guineapig the M L D is 40 mg, compared with 1 mg of Russell viper venom The venom of *Vipera berus* contains a small amount of neurotoxin to paralyse its prey and facilitate swallowing it whole Hæmorrhagins are also present Hæmorrhagin has a special affinity for the endothelial cells of the capillaries, causing lysis of the cells and subsequent hæmorrhagic œdema or small petechiæ, sometimes a canary-yellow discoloration of the skin spreads up the course of the lymphatics, and in 1 of Morton's cases this involved the whole upper limb In his series no sloughing of tissues was seen, so the cytotoxins which are partly responsible for the œdema are not very powerful

The best and safest first-aid treatment is to delay the absorption of the toxins up the lymphatics—in the upper limb by a sling and bandage, and in the lower limb by tying the two legs together and keeping the patient in the recumbent posture The results of an adder-bite are completely unpredictable since they depend on the amount of venin injected and on the age and constitution of the patient The local effects are constant in kind but variable in intensity General effects may be negligible in adults The earlier the onset of such effects the more severe will these be and the greater the local reaction to the bite In severe reactions giddiness, sweating, collapse, and severe persistent vomiting ensue within the hour, and Morton finds that, if these symptoms have not developed within two hours after the bite, no antivenin is necessary rest, reassurance, and the administration of an antihistamine drug at intervals of from four to six hours is all that is required

The old-fashioned tissue-damaging measures, such as the tourniquet, incisions, and suction, rubbing in potassium-permanganate crystals, and infiltration with 5% carbolic soap, have no place in the treatment of adder-bites in this country The antivenin available in all public-health laboratories is the Pasteur Institute E.R. serum in ampoules of 10 ml for neutralising the venoms of vipers in France (*Vipera berus* and *Vipera aspis*) This should be given subcutaneously in the vicinity of the bite, if the anatomical site allows, but never in the fingers or toes Since most bites are on the fingers, and the cases are rarely seen early the serum must often be injected intramuscularly into the buttocks Serum sickness develops commonly, despite administration of anti-histamine drugs The antivenin controls the general symptoms in from two to twelve hours after its administration, and in only 1 case in Morton's series was it necessary to give glucose-saline intravenously on account of shock

Morton calls for propaganda in the Press, through television, and in the schoolroom to bring this holiday hazard to the notice of the public

ARTHROPOD-BORNE VIRUSES

IN Britain our wont is to complain about the weather, but it is worth considering some of the advantages of our temperate, if uncertain, climate One advantage is our almost complete freedom from virus diseases spread by the bites of blood-sucking insects The Scots and the Irish may occasionally be bitten by ticks which carry the virus of louping-ill, and may then have a mild influenzal illness or a more serious disease resembling poliomyelitis, but in England we seem to be free from all such hazards Our good fortune is the more remarkable because more than a hundred distinct animal viruses are spread by arthropods—mostly mosquitoes Where do all these viruses come from? How important are they as possible causes of disease in man? These and other questions were discussed at a symposium held by the Royal Society of Tropical Medicine and Hygiene [1]

Prof C D Darlington suggested that as regards the virus the distinctions between animals, insects, and plants were not fundamental, but that the fundamental distinction was between the form of nucleic acid which was the basis of propagation He contrasted the mechanism whereby the genetic apparatus of an organism was passed on to its descendants and the means by which infection was transmitted from one organism to a second He suggested that vectored viruses of animals and bacteriophages were examples of double systems of propagation which depended on both heredity and infection

Mr P F Mattingly developed the thesis that the arthropod-borne viruses arose in their arthropod vectors Within the insect they might have arisen de novo or by parasitic degeneration from higher forms—possibly rickettsiæ In either case it seemed probable that the present form was developed in association with the

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[1] Morton T C Brit med J July 30 1960 p 373

[2] See Lancet, 1957 i, 1075

[1] Trans R Soc trop Med Hyg 1960 54, no 131 see Lancet 1960,

lution of blood-sucking habits by arthropods Most of
vectors of these agents are species of culicine mos-
toes which are primarily bird-feeders He therefore
gested that the earliest forms had arisen in culicine
squitoes and in birds, and that spread to mammals was
ter development He emphasised the importance to the
us of hibernation or æstivation of mosquitoes in sub-
pical areas where climatic conditions limit mosquito
ivity

Dr C E Gordon Smith declared that many arthropod-
rne viruses were not known to cause any disease in man
t that man could become infected by intruding into
tain ecological backgrounds, as in the case of human
ections with "jungle" yellow fever

Dr C H Andrewes supported Mr Mattingly's view
it the arthropod-borne viruses probably arise in
ociation with their insect vectors, but suggested that
tick-borne viruses were more primitive than the
squito-borne The transovarial transmission of viruses
the Russian spring-summer encephalitis group (which
ludes our virus of louping-ill) indicated a very old
rtnership between tick and virus

Prof D S Bertram suggested that the explanation of
insovarial transmission with ticks but not with mos-
itoes lay in the presence in the former of only one
embrane separating the ovary from the hæmocele,
ereas in mosquitoes there were three such membranes

Dr J S Porterfield cited virus isolations in Uganda
d Israel which could be interpreted as denoting that
inor antigenic changes were taking place quite rapidly
present. Dr P B Stones advanced the hypothesis that
arbor viruses were evolved from mosquitoes one might
pect to isolate viruses from male mosquitoes as well as
om females, and reported the isolation of one virus from
ale mosquitoes collected in the British Cameroons Dr
H A Sneath, arguing by analogy from bacteriophages,
ggested that an arthropod-borne virus might obtain
rt of its genes from an insect, part from a bird, and part
om a mammal.

The symposium raised important issues, some of which
ay be settled by further experimentation in the labora-
ry It did not explain our freedom from infection with
ruses of this group, but prompted the thought that
rtain undiagnosed "virus fevers" in this country may
e due to unrecognised infections with arthropod-borne
ruses

RESECTION FOR PULMONARY TUBERCULOSIS IN THE ARMY

THE 500th resection for pulmonary tuberculosis was
one at the Army Chest Centre at Hindhead on June 7
f these operations, 137 were on Gurkhas and form part
f an intensive effort, begun three years ago, to eliminate
uberculosis from the Brigade of Gurkhas[1] Judging by
he decline in the number of cases during the past year,
his campaign is proving successful

Normally, or course, pulmonary tuberculosis is nowa-
lays treated by chemotherapy, and surgery is seldom
eeded Outsiders may wonder therefore why the Army,
with its relatively small population, should have so large
record of resections In point of fact, since the first
major thoracic operation was performed at the Army
Chest Centre some seven years ago, a consistent policy
has been followed, and resection has been limited to
those segments or lobes (or even wedges) in which
the disease has failed to clear after a reasonable period of chemotherapy (Thus 16 Gurkhas have been sent back to Malaya without operation because the disease had resolved sufficiently to make surgery unnecessary) But in deciding what is a "reasonable" period the facts of military life have had to be recognised In the Services it is not always easy to provide the long-continued specialised aftercare sometimes needed for patients treated by chemotherapy alone The man who remains under treatment may suffer from a stigma both in the mind of others and in his own If there is only one lesion in his lung and it can be removed, the operation will restore his morale and help him to take his place again with renewed confidence in an organisation which, a few years ago, would have promptly discharged him as unfit Morale in the soldier is constantly emphasised, and the Army Chest Centre has played a part in keeping it high.

Such a policy can stand only if the results of surgery seem to justify it 2 patients died, but 1 of them was a man of 44 who had a massive myocardial infarction ten days after operation, and the only death associated with the operation was that of a man of 21 whose postoperative hæmorrhage may have been due to afibrinogenæmia The incidence of complications, too, was remarkably low It says much for the Army Medical Services that this specialised surgery should be done with such success under their auspices with the cooperation of civilian consultants

HOW MANY AUTOCLAVES?

ON page 643 of our present issue, Prof Charles Wells and Dr Francis Whitwell emphasise the remarkable output of a modern high-vacuum surgical steriliser if it is properly used It is not yet appreciated how much more efficient is sterilisation by such instruments than by older less efficient sterilisers, especially when these were operated—as they often were—by methods which left something to be desired[1–5] We may get a firm grip of this important matter by looking at the situation described by Wells and Whitwell Before the sterilising process of a particular 650-bed hospital was modernised, the work was done in one large rectangular 72 c ft autoclave in which steam penetration was accomplished by downward displacement of air and the drawing of the usual preliminary partial vacuum The weekly load averaged 1000 dressing-drums and 110 glove-drums Every weekday the requirement of the hospital was for three loads of dressing-drums, each load requiring 160 minutes for its sterilising cycle, and one load of glove-drums, requiring 90 minutes This work, together with the collecting and distributing of drums, required a team of two orderlies, one or other of whom worked daily from 7 A M to 9 P M with shorter hours at weekends Observations reported from other hospitals[1–5] have now taught us that similar procedures seldom carried a good guarantee of sterility and that the risks accepted by deliberate under-treatment of gloves were not always free from tragic results When modernisation was contemplated in the hospital referred to by Wells and Whitwell, forecasts of the capacity of the steriliser that would be required for the loads described ranged from 16 to 38 c ft In the event, the output of a modern high-pressure, high-vacuum autoclave of 3½ c ft capacity came so near to meeting the needs of the hospital that the two orderlies, working in shifts from 7 A M to 10 30 P M, were able to get through the work

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[1] *Lancet*, 1958, ii 1053

[1] Bowie, J H *Pharm J* 1955 174 473
[2] Howie J W, Timbury M C *Lancet*, 1956, ii, 669
[3] M R C Report, *ibid* 1959 i 425
[4] Nuffield Provincial Hospital Trust (1958)
[5] *Lancet*, 1959, ii, 178

This remarkable demonstration, of course, is to be taken rather as a measure of increased efficiency than as a model of how these things should be arranged For the type of hospital and work with which they were concerned, Wells and Whitwell think that an instrument of 9 or 10 c ft would be ideal in that it would allow a reasonable loading schedule, shorter shifts, and some expansion of work All who are equally worried by present doubts about their sterilising methods and where the money is to be found for new apparatus may take heart from the facts disclosed Obviously if the increased efficiency is of such an order that a steriliser of 10 c ft may do more work, and do it much more reliably, than one of 72 c ft the cost of safety is not to be nearly so great as at first glance it might appear to be Moreover, as we recently remarked,[6] if hospitals will get together to rationalise their sterilising procedures in central sterile supply departments, still further advantages will accrue in the form of more highly skilled operators, better supervision, easier maintenance of sterilisers, and better arrangements for dealing with sudden emergencies In general, big sterilisers, even of the modern high-vacuum, high-pressure type, are not to be recommended The smaller-capacity instruments, of 25 c ft or less, obviate many difficulties of maintenance and make it far easier to get rid of the small amounts of air which remain even after a high vacuum has been drawn and whose displacement is essential in order to guarantee steam penetration into all parts of the load

One further point in the valuable report of Wells and Whitwell deserves comment—namely, that rubber sheeting is not easily sterilised even in a highly efficient steriliser This observation is in agreement with other unpublished experiences and it emphasises that the nature of rubber sheeting renders its sterilisation by steam in an autoclave a very difficult matter In fact many supposedly sterile rubber sheets have proved to be as highly contaminated as the unsterile areas they were intended to cover What is equally dangerous a rubber sheet in a load may prevent adequate steam penetration to articles other than itself We need to consider acceptable alternatives to rubber sheeting or more reliable methods of guaranteeing its sterility

THE VERY DEAF CHILD

DURING the past fifteen years much progress has been made in training the hearing of the deaf child, yet the standard educational classification of deaf children in this country is still that laid down by the Board of Education's committee of inquiry in 1938 Though recent advances have made the whole classification out of date, many teachers of the deaf still regard it as sacrosanct and are horrified by any change from the recommendations of twenty-two years ago For example, the Association of Non Maintained Schools for the Deaf lately sent us a resolution which said

> It has come to the notice of this Association that Grade III deaf children are being placed in Units for Partially Hearing Children, a move which is detrimental to the education of the severely deaf child It is the unanimous opinion of this Association borne of long experience that all Grade III d children of any age should be placed in schools for the d

The medical reader may ask ' What are grade III d children ? " The definition by the Board of Educa Committee was

> " The children in this Grade can hear and understand c versation at not more than 2 feet, if at all, though they ma able to hear vowels, with or without distinguishing betw them, at distances greater than 2 feet Their hearing loss is c 40 decibels (G A) or 60 decibels (P T A) and may be total Th speech and language, if any, are seriously defective, because of their loss of hearing, cannot be developed except the methods of teaching applicable to deaf children who h not acquired speech and language naturally This Grade d not include any children, no matter what their hearing l whose speech and language development are not seri defective The hearing of few children of this Grade can improved by medical treatment, but many can be helped the use of hearing aids "

The fallacy of this definition is the assumption that if t deaf child has not developed speech naturally by the ti he is tested he never can and never will do so Rec experience in many countries has shown that unbelieva small remnants of hearing can enable the child to lea speech through hearing if he is given the right help at t right time [8–13] The first tests of hearing may show comprehension of speech and only the ability to respo to vowel sounds and noises, but if auditory training started, and the child is tested again after an interval, will be found to have an apparent improvement in hearin Even the pure-tone audiogram improves with trainir This improvement is not a " cure " of the deafness, it an improvement, through learning, in the perception a discrimination of sounds

Failure to appreciate the apparent change in heari which may follow training is the main reason why spec schools are recommended as preferable The value such auditory training can be denied because its ve success destroys the evidence of profound hearing lo In contrast the non-auditory methods in special scho for the deaf preserve the hearing loss of the pup unchanged

The apparent change in hearing which is so dramatic the deaf child is similar to the change that takes pl every day in the hearing of the normal infant The ne born infant cannot " hear and understand conversation at 2 feet or any other distance He has to learn the mea ing of sounds, and he does this gradually during the f years of life—producing his first attempts at comprehe sible speech after about a year of listening Because h hearing is normal he can hear sounds easily and th learning process goes on without specific help—' spo taneously ' The deaf infant depends on others to enab him to hear sounds loud enough and often enough for th learning process to take place the sounds must be utter into the ear, or (better still) he has a hearing-aid Wi out this opportunity he will be dumb, with it he w develop speech, not so easily as the normally heari infant, but by the same type of learning process If t diagnosis is made early enough, in the first few months life, and adequate auditory stimuli are provided, spe will develop almost ' spontaneously " and subseque admission to a school for the deaf is unthinkable

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6 [illegible]

7 [illegible] Committee of Inquiry into Problems relating to Children with Defective Hearing [illegible] H M S [illegible] 19

8 Hardy W G Pauls M D Bordley J E [illegible] 1951 [illegible] 40 [illegible]

9 [illegible] D [illegible] 1951 [illegible] 53

10 [illegible] 1951 [illegible]

11 [illegible]

12 [illegible] D B [illegible] 1951 i, 553

13 [illegible] 1951 ii, [illegible]

Public Health

IN-SERVICE MENTAL-HEALTH TRAINING FOR HEALTH VISITORS

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The Working Party on Health Visiting (1956) described health visitors as "general purpose family visitors" concerned largely with health education and social advice, and it recommended that they should undertake combined duties in public-health and medico-social work

Edinburgh has about a hundred health visitors The optimum number has not yet been recruited, and the present proportion is nearly one to every 4300 of the population Progress has recently been made towards broadening the scope of health visitors' activities by combining duties in such a way that each is concerned with a whole range of services—antenatal, child welfare, school health, tuberculosis, and care of the aged—and thus becomes the general adviser to families in her own district

The health visitor, being a registered general nurse with additional qualifications in midwifery and social medicine, may come in contact with a family through meeting the mother at an antenatal clinic, by regular visits to the home to see mother and baby, or through seeing the child at school Contact at a later stage may arise in special circumstances—e g , through tuberculosis or through one of the increasing number of old persons receiving supervision

In addition general practitioners or hospital doctors may may refer patients to the health visitor A health visitor is now attached to midwifery, pædiatric, and geriatric hospitals in Edinburgh to ensure, wherever necessary, adequate liaison and appropriate assistance in the rehabilitation of patients and in providing information on their home background All these duties are performed in cooperation with the family doctor Thus, inevitably, the health visitor comes in contact with psychiatric problems

In view of the reorientation of the health visitors' field of work and the modern conception of community mental-health care, it was thought desirable to discover the extent to which mental-health care and aftercare could be included in health visitors' duties It was necessary first to decide how the health visitor could best play her part without overlapping with other social workers An important step seemed to be to increase contact between the local authority and hospital staffs, to foster mutual confidence and knowledge of each other's work Information was sought on how best to give the health visitor more insight into the care and management of the mentally ill in the community A basic knowledge of this work seemed likely to bring a more enlightened approach to prevention and ascertainment of mental breakdown at an early stage The end result, it was hoped, would be a close integration of the services

The experimental course was started in September, 1959 The hospital concerned in the training scheme is responsible for a population of about 170,000 people living in the southern and eastern parts of Edinburgh Some thirty health visitors work in the homes and clinics in this area, and the majority were already doing combined duties The health visitors (ten in number) who took part in the course were from the area immediately around the hospital, and each had about 400 families on her visiting-list The superintendent of health visitors joined the course A similar course for the other health visitors working in the hospital catchment area is planned to start shortly

OUTLINE OF THE COURSE

The course, which was expected to continue for at least six months, comprised weekly lectures and discussions, with some clinical demonstrations and visits to various parts of the hospital A preliminary aim was to make the health visitor feel at home with the psychiatrist's approach and the hospital "jargon" Small groups of health visitors attended the staff clinical conferences each week In this way the health visitor would come to realise the various needs of the mental-hospital patient, and some cases would be allocated for aftercare It was arranged that one of the health visitors would act as "liaison health visitor" and would attend two additional ward conferences each week to discuss whether potential referrals were practicable Arrangements were made for health visitors and the senior psychiatric social worker to discuss problems arising in the supervision of patients in the community Each *health visitor spent a short period in the women's admission* ward of the hospital to gain more complete insight into psychiatric nursing and treatment Since the lecture-discussions were completed, there have been monthly meetings of the health visitors with the psychiatrist, the senior medical officer for mental-health services, and the hospital psychiatric social workers to discuss any administrative or clinical difficulties

CONTENT OF THE COURSE

The course started with an introductory talk and discussion in the health department at which the senior medical officer for mental-health services outlined its purpose and plans Afterwards there was a series of eight lectures by the psychiatrist, each lasting about forty minutes, which included history of the management of the mentally ill, psychological concepts, the treatment of recent admissions, rehabilitation of long-term patients, and administrative and medicolegal arrangements Some stencilled lecture notes were provided Each lecture was followed by a visit to a department of the hospital to illustrate the subject, and then a discussion took place over coffee with the psychiatric social workers and the matron or her deputy The health visitors attended electroconvulsive-therapy sessions and the hospital case conferences in groups of two or three, on rota After a talk by one of the psychiatric social workers on the functions and arrangements at the outpatients' social club a rota was arranged for the health visitors to attend in the evening

By the ninth lecture, when the health visitors were initiated into the atmosphere and technical language of the hospital, it seemed opportune to invite the staff of the department of psychiatric social work and their students to join the meetings The routine of the sessions was changed to an introduction and clinical demonstration of a particular psychiatric syndrome, followed by a discussion of its implications on the work of the health visitor and the psychiatric social worker Copies of *Essentials of Case Work* (1957) were distributed, and this was discussed over the weeks with regard to the role of the health visitor in psychiatric cases

The health visitor was now able to attend the wards as a nurse with at least some theoretical knowledge of psychiatry She worked from 9 A M to 1 P M for six days, and found scope for her knowledge of physical illness as well as better orientation in mental nursing Apart from her practical ward work, each health visitor spent about one and a half hours a week in the hospital

During the course the psychiatrist accompanied each health visitor on one of her district rounds The 4–6 cases visited were selected by the health visitor to represent a fair sample of her routine, and to include one or two with definite psychiatric bias The visits also included child-welfare centres and school clinics The psychiatrist thus became acquainted with the health visitor's routine and had the chance to observe her approach to patients Later, the psychiatric social worker also accompanied the health visitor on her round to gain insight into her work

RESULTS

As the course was exploratory and the experiment is still incomplete, the results are limited and the conclusions must be tentative But the course has been judged helpful by both local-authority and hospital staff in view of the following achievements

1 *Health visitors have gained insight into psychiatric states, diagnostic problems, management, and mental nursing*

2 *Health visitors and psychiatric social workers have collaborated in the care of certain cases to their advantage and to the benefit of the patient*

Exchange of information on psychological and physical aspects was of value to all It was useful in some cases to arrange joint visits by psychiatric social workers and health visitors for a while before the health visitor continued alone

3 *A number of psychiatric patients have been referred to health visitors for supervision and aftercare*

During the first nine months of the scheme the health visiting service throughout Edinburgh undertook some supervision and investigation of 35 women and 12 men These patients had been admitted to hospital recently or were under consideration for discharge Very few were old people The allocation of patients was not limited to members of the class In about half the cases the work was undertaken in collaboration with the psychiatric social worker The cases were selected by the doctors, psychiatric social workers, and liaison health visitor at the ward conferences The health visitor for each case was then invited to the hospital to meet the patient and to get background and clinical information from the doctor in charge of the case and from the psychiatric social worker In a few cases information only was contributed—e g , from the knowledge of health visitors or others from local-authority departments who had dealt with the patient in the past This information was often produced more efficiently by the liaison health visitor than any other way

Clinically the largest number of patients referred had "depression", but patients with schizophrenic and paranoid illnesses responding to phenothiazine drugs were also included Several patients had physical complications—e g , diabetes, disseminated sclerosis and hemiplegia 3 had concurrent pregnancies In some cases the health visitor was already visiting the home because of young children or because the patient had tuberculosis

4 *The health visitor has from time to time contributed relevan valuable information at case conferences and discussions*

5 *Administrative mechanisms have been worked out for appropri referrals and information to be passed expeditiously between services*

As the role of the health visitor is at present controversia and as it was planned to extend her function into the obvio territory of the psychiatric social worker, special care had to taken to uphold the status of both professions Referral patients to health visitors only after discussion with t psychiatric social worker, and with direct responsibility to t doctor, satisfied the interprofessional needs and was at the sa time practical from the clinical point of view

The psychiatric social worker must have records which ind cate changes in the patient's circumstances and problem Difficulties of communication arise from the health visito mobility after her initial daily contact with headquarters at health department As the doctor deals with several soc workers, lists are necessary to indicate the up-to-date distrib tion of the cases allocated to each worker The liaison heal visitor is a convenient person to transmit brief reports on beh of her colleagues at the additional ward rounds which s attends

6 *A greater understanding of the functions of each is fostered collaboration between the public-health and hospital services*

The liaison health visitor at the ward conferences, and t accompaniment of each health visitor on her round, have giv the doctors a wider and clearer conception of the functions local-authority departments, and have enabled both docto and psychiatric social workers to achieve better workin relations with them

DISCUSSION

If the health visitor is to be a general family advise she must have a wider knowledge of the clinical and soci problems related to mental illness When the psychiatri and psychiatric social worker accompanied the healt visitors on visits several psychiatric cases were seen Th most frequent diagnoses were mental deficiency, anxiet states, and inadequate or neurotic psychopathy, bu patients with senile and frankly psychotic states were als visited In these circumstances a study by a healt visitor of psychiatric patients and modern psychiatr treatment is not only desirable but necessary Furthe more, closer association between health visitors an specialists in mental health is necessary if health visitor are to educate the community in mental health

The health visitor must also be familiar with the les attractive aspects of the local mental hospital, and be abl to differentiate fact from fantasy in ex-patients' reports The health visitor can be invaluable in these day when mental hospitals still need ambassadors in th community

The cases so far referred have been carefully selecte and did not include difficult psychotic, psychopathic, o neurotic patients requiring special skills in managemen Several cases had physical complications in which th nurses' previous training was relevant Where visiting b both psychiatric social worker and health visitor wa necessary, the closer liaison and understanding helpe considerably

One aim of the experimental course was to try to solv the problem of multiple family visiting This was achieve even where both psychiatric social worker and health visitor visited the patient at first In general it is desirabl that any patient coming into a mental hospital who ha been visited previously at home by a health visitor should if possible, still be under her care for the psychiatric side ıe full history of new cases, however, should still be :en only by the psychiatric social worker, though, of ırse, health visitors should supplement the social 'estigations

Another point is worth mentioning Professional ırkers must appreciate that patients tend to classify them d give them what they regard as the appropriate infor-ıtion Some may be irrationally anxious about the ormation to be passed on, or suspicious of visits made health visitors on behalf of the mental-health services, [1] the purpose of the visit is explained

Finally, some health visitors may feel unable to accept e new and varied responsibilities of mental-health work, d others may not be suitable in temperament and rsonality, Hence both voluntary withdrawal from hemes such as this, and adequate selection procedures, ust be arranged

Our thanks are due to Dr T A. Munro, physician-superintendent, d Miss J MacLeod, matron, the Royal Edinburgh Hospital, for ır encouragement, helpful cooperation, and advice

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Arsenical Haulm and Weed Killers

This is the last year in which arsenical haulm and weed killers will be used The Ministry of Agriculture, Fisheries, and Food declares that farmers and their workers should be on the alert until the potato crop is safely stored and contaminated vegetable rubbish has been rendered harmless

Certain precautions are required by *law* workers preparing and applying the spray must wear protective clothing, and potato pickers must wear special protection if the crop is lifted within ten days of spraying

Before spraying, warning notices should be erected at gates, unprotected persons should be deterred from entering the fields There is a serious risk to livestock if fences are not stock-proof

Serious accidents have been caused by water-supplies becoming contaminated during preparation of the spray Spray tanks should always be filled in the field where they are to be used, and great care is needed to prevent spilling When cleaning the machinery, attention must be paid to safe disposal of the washings Care is also needed to ensure safe storage of full containers of the concentrate Empty containers should be punctured to prevent further use and be burned, buried, or otherwise disposed of safely

African Horse Sickness

The epizootic of this disease which is now in progress in the Near and Middle East[1] has spread to Cyprus At the weekend [2] 30 to 40 animals were reported to have died Cypriot officials have asked the United Nations Food and Agriculture Organisation in Rome to send preventive vaccine

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1 *Lancet*, July 9, 1960, p 84
2 *Times*, Sept 12, 1960

Special Articles

A SMALL AUTOCLAVE IN A LARGE HOSPITAL *

CHARLES WELLS
M B Lpool, F R C S
PROFESSOR OF SURGERY IN THE UNIVERSITY OF LIVERPOOL

FRANCIS R WHITWELL
M D Lond
PATHOLOGIST TO BROADGREEN AND AINTREE HOSPITALS, LIVERPOOL

Broadgreen is a general hospital of about 650 beds t includes a maternity unit of 90 beds, about 200 general urgical and gynæcological beds, the regional thoracic unit f 100 beds, about 90 orthopædic beds, and a small aciomaxillary unit There are five busy operating-heatres

he Old Autoclave †

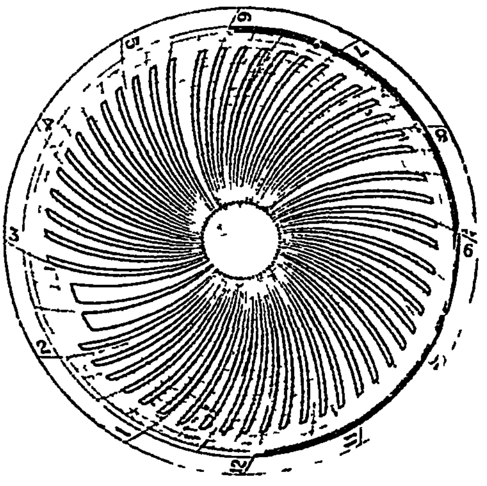
Until November, 1959, all the hospital autoclaving of lressings, gowns, towels, swabs, and gloves was done in ıne large rectangular downdraught-displacement auto-:lave of 72 c ft capacity, drawing the usual partial 'acuum The weekly load averaged 1000 dressing drums ınd 140 glove drums Every weekday three loads of lressing drums, each lasting 160 minutes, and one load of glove drums, lasting 90 minutes were required, The ıutoclave was operated by one member of a team of two ›rderlies working from 7 A M to 9 P M The duties of this :eam also included collecting and distributing drums At weekends, when there were fewer loads, shorter hours were worked

In the summer of 1959 it was decided to remove the ıutoclaving from a room in the theatre suite to a separate department, and to consider replacing the large autoclave by a smaller high-speed high-vacuum model Five manufacturers of such equipment were consulted, given the weekly drum turnover, and asked what size of machine would be needed Their replies varied from 16 to 38 c ft

The New Autoclave

In November, 1959, a local manufacturer lent the hospital the prototype of a high-speed high-vacuum cylindrical autoclave of $3^1/_3$ c ft capacity A number of minor modifications were made by the manufacturer, and for the last three months the instrument has given continuous service at a phenomenal rate of turnover

The machine has two fully automatic cycles—one for dress-



An untouched reproduction of a typical 12-hour time/temperature recorder chart, showing the total number of complete cycles between 8 0 a.m. and 8 0 p m (fifty-three dressing loads and two glove loads)

A larger-scale continuous strip record could be more easily read with such short runs ings and one for gloves It can also be worked by hand, although it has not been used in this way The dressing cycle is

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* A report to the Medical Research Council Working Party on Pressure-Steam-Sterilisers

† " Autoclave " is not a strictly accurate term but is convenient and well understood

1 About 3 minutes to draw prevacuum down to 0 8 in (20 mm) positive pressure—i e , 29 2 "inches of vacuum" at 30 in Hg atmospheric pressure (holding-time nil)

2 About 1 minute to attain 276°F (135°C) at a steam pressure of 32 lb per sq in (holding-time 3 minutes)

3 About 2 minutes to draw postvacuum 1 6 in (40 mm) Hg (holding-time nil)

4 About $^{1}/$ minute to break the vacuum

Approximate total for cycle = $9^{1}/_{2}$ minutes

An absolute-pressure switch is fitted to ensure that the cycle cannot change until the correct degree of vacuum is obtained

An integrator is fitted which maintains a predetermined relation between time and temperature throughout the sterilising part of the cycle Opinions differ about the need for this rather expensive piece of apparatus Under ideal conditions the optimum temperature is quickly reached, and the holding-time can then be simply measured If the main steam supply is variable, however, and especially if the chamber is large, the predetermined pressure and temperature may be reached more slowly In these circumstances the integrator makes allowance for the sterilisation effected by the steam as it is building up to the predetermined pressure and temperature In addition, the integrator compensates for the small variations in pressure that may arise if the main steam supply is less than perfect In this particular autoclave, and at this particular hospital, the integrator is probably unnecessary, but it is a standard part of the 'Drayton' control system

The glove cycle is the same as the dressing cycle, except that a steam pressure of 17 lb per sq in (251°F or 121°C) is held for 15 minutes

Our original aim was merely to test the efficiency of the autoclave using thermocouples, Browne's tubes, and spore papers, for differently packed drums during both cycles But, the early results were so satisfactory that in addition we have tested the mechanical reliability of the machine by overusing it We have, at the same time, gained valuable and rather surprising information about the possible turnover with a chamber as small as $3^{1}/_{2}$ cu ft

THE TESTS

Thermocouple tests gave results within the chamber identical with those recorded by the machine

Browne's Tubes, type 1 (black spot), as is already known, do not change to a true green with high-speed processes because there is not long enough for the chemical reaction to occur Browne's tube, type 2 (yellow spot), is now known to be suitable for use in high-vacuum high-pressure sterilisers for both gloves and dressings One tube was put into at least one drum of each load, and a tube was also put into each large chest-unit drum The results were satisfactory except for occasional large chest-unit drums containing heavy rubber sheets

Spore tests were made fortnightly on dressing and drum cycles using *Bacillus stearothermophilus* All spores were killed except those in one large chest-unit drum containing rubber sheets

Moisture —Only occasional large drums from the chest unit, with the rubber sheets mentioned above, failed to dry completely

Mechanical reliability and capacity —For over 3 months this instrument has daily autoclaved about 160 dressing drums (in about fifty loads) and 24 glove drums (in three loads) It is managed, in shifts from 7 0 A M to 10 30 P M by one operator of two, whose duties include collecting and delivering drums in the hospital, as before

Thus, this one small machine is handling 90% of the total hospital work, although the operator's hours have needed to be increased by 10% Obviously, this rate work is undesirable, probably overstraining the m and certainly overworking the operator who has to load and unload five times an hour, but it proves conclusively the enormous capacity of the new machine

CONCLUSIONS

1 We find this machine very satisfactory

2 Cylindrical autoclaves have definite mechanical and cost advantages over rectangular ones We do not concur with those who think, that from the user's standpoint, a rectangular chamber is so far preferable as to outweigh the undoubted mechanical and cost advantages

3 A suitable size of autoclave of this type, for this hospital and allowing for some expansion of work, would be 9 or 10 c ft This would reduce the loading and unloading to four times an hour, and allow the operators to work shorter shifts

4 We are not convinced that a separate glove cycle is necessary We have evidence which suggests that gloves autoclaved in the dressing cycle last quite as long as those done in the glove cycle Further experiments are needed, and these are being made

5 Large drums are undesirable, and we have shown that large rubber sheets are relatively difficult to sterilise For many reasons, including the efficient packing of the chamber, individual packs should be brought into routine use in place of drums

6 Large rubber sheets should not be used

We are indebted for the fullest possible cooperation and assistance to the Liverpool Regional Hospital Board and the hospital management committee, and to Messrs Henry Wilson, of Cornhill Works Kirkby, Liverpool, who made and supplied the autoclave

Conferences

NEPHROLOGY

THE 1st International Congress of Nephrology was held at Evian from Sept 1 to 4

Tubular Function

It was suitable that H WIRZ should give the first paper, for much of the subsequent work that was presented confirmed and elaborated the brilliant hypothesis which he, together with HARGITAY and KUHN, first proposed about ten years ago It now seems a generally accepted view that the counter-current of fluid in the medulla is involved in the mechanism of urine concentration R W BERLINER and others, including C W GOTTSCHALK, W E LASSITER, M MYLLE, K J ULLRICH, B SCHMIDT-NIELSEN, G PEHLING, and R O'DELL presented evidence which supported the counter-current hypothesis They have extended Wirz's original observations and shown that the fluid at the tip of the loop of Henle remains hypertonic when the urine is hypotonic, that urea is reabsorbed from the collecting ducts during antidiuresis, and that water is reabsorbed throughout the whole length of the nephron including the loop of Henle, whether the final urine is hypotonic or hypertonic Perhaps the neatest confirmation of the countercurrent hypothesis was the demonstration by F MOREL and M GUINNEBAULT that if radioactive sodium and tritiated water are injected simultaneously into the renal artery, and the kidney removed a minute later, the sodium is seen to be trapped in the medulla, there being little or none in the cortex, whereas the tritiated water is only present in the cortex

W Gottschalk et al. also found that during an osmotic ress the fluid obtained from the proximal tubule had a d-to-plasma sodium concentration ratio of approximately 5—additional evidence for active sodium reabsorption in the ximal tubule. There was general agreement, in accordance h the findings of E. M. Darmady and his colleagues with elled vasopressin, that antidiuretic hormone (A.D.H.) must on the distal and collecting tubules and that it probably nges the permeability of the tubule wall. There was some cussion whether, in addition, A.D.H. might not alter the rate blood-flow through the medulla and so influence urine centration. L. S Lilienfield and H. C. Maganzini, vever, using one technique for measuring medullary blood- w, and K. Kramer and K. J Ullrich using another, tained completely contradictory results when estimating the nge in blood-flow when urine concentration changes It was sant to hear that the two sets of workers were now working gether to try to resolve their differences J B Longley, S Burstone, N A. Lassen, W G Banfield, and D C. ndley showed that the afferent limb of the vasa recta is ch thicker than the efferent limb They were able to tinguish the afferent limb because of its content of esterase ich allows it to be stained differently from surrounding uctures

Stop-flow Technique

One morning was spent discussing the stop-flow technique R. L. Malvin, W S Wilde, and Sullivan—a manœuvre at Pitts has called the "poor man's micropuncture" E. llman and F Morel both presented evidence that glomeru- r filtration continued throughout the time that the ureter was ructed. It was generally agreed, therefore, that this tech- que can perhaps give some information about distal tubular ction but that it is an unsafe guide to proximal tubular func- n. The results obtained on fluid considered to come from e distal and collecting tubules are in keeping with evidence tained by micropuncture. The neatest variation on the stop ow technique was described by D E. Oken He places fluids f known composition in selected parts of a nephron with a icropipette, the fluid being prevented from moving away om this site by being wedged between two drops of oil. fter varying intervals the fluid is removed and its content alysed. His evidence confirmed that of Morel obtained by rdinary micropuncture techniques that potassium appears be moved passively into the lumen of the tubule by passing long an electric potential gradient.

Potassium Metabolism

S W Stanbury gave a masterly review of the relation of the dney to potassium metabolism. He pointed out that the intra- llular content of potassium is an important factor in the dney's ability to excrete potassium, and that, as the adminis- ration of potassium to sodium-deficient patients increases odium excretion, potassium can probably interfere with odium reabsorption, perhaps in the proximal tubule. He sted the conditions in which excessive potassium excretion ccurs and underlined the work of J W Mills, S Thomas, nd K. S Williamson who have found that aldosterone ncreases potassium excretion while decreasing hydrogen-ion excretion, whereas cortisol increases potassium excretion with- out changing hydrogen-ion excretion. F C. Bartter discussed the various mechanisms known to influence the secretion of dosterone, including hæmodynamic factors, total body- potassium, corticotrophin, and changes in the electrolyte concentration of the blood perfusing the adrenals In addition he had recently found that intracarotid infusion of potassium could also cause a rise in aldosterone secretion, though the same amount given intravenously had no effect. Hypophysec- tomy abolished this change. He then described what sub- sequent speakers called Bartter's syndrome. He had only one case—a boy with a renal leak of potassium associated with creased aldosterone secretion and adrenal hyperplasia. Renal biopsy showed gross hypertrophy of the juxtaglomerular apparatus, which in many glomeruli had invaded and obliterated the glomeruli. The implication that some substance elaborated by the juxtaglomerular apparatus might have stimulated aldosterone secretion was not mentioned, though it hung heavily in the air It was supported later, when J Laragh demonstrated that an infusion of angiotonin raised aldosterone secretion. It seemed as if once again a patient had presented an invaluable clue.

Aldosterone Secretion

A. F Muller pointed out that the upright posture increased aldosterone secretion, and that the usual diurnal rhythm of aldosterone secretion, therefore, was often abolished if the person stayed in bed. He discussed what is now known as the "escape" mechanism to aldosterone—that is, the ability of a healthy person to regulate urinary sodium excretion and maintain a steady sodium balance while being given a constant infusion of aldosterone. This "escape" mechanism cannot be demonstrated in patients with hypopituitarism or œdema. He emphasised that the increased aldosterone excretion in œdematous patients is perhaps only a small factor contributing to the œdema. His results showed that there was no relationship between the increase in sodium excretion which might follow the administration of spirolactone and the rate of aldosterone secretion immediately preceding its administration. He confirmed Shaldon, McLaren, and Sherlock's findings that a most effective way to produce diuresis in patients who are resistant to the usual methods is to give a combination of chlorothiazide and spirolactone.

Acid Urine

W B Schwartz discussed the ability of the kidney to form an acid urine and the changes in the rate of urinary excretion of titratable acid, ammonia, and bicarbonate in chronic renal failure and renal tubular acidosis His main point—that a bicarbonate leak was a primary cause of the systemic acidosis in both conditions—was severely challenged by D W Seldin, who pointed out that, if for some reason there is a primary impairment of the ability to acidify the urine, bicarbonate excretion must continue, and that the leak of bicarbonate in such a circumstance is not evidence of impaired capacity to reabsorb bicarbonate. This objection to Schwartz's conclusions applied particularly to patients with renal tubular acidosis.

The Kidney in "Shock"

From this discussion it was clear that the word "shock" means as little in the rest of the world as it does in this country and that semantic clarity would best be served if it ceased to be used. P Vassalli described a "shock kidney" as acute renal failure due to acute reduction in renal blood-flow whether or not there was any clinical evidence of "shock", whereas M. Legrain's description was acute renal failure accompanied by an undefined "vascular collapse" One outstanding fact emerged it was agreed that once acute renal failure was established the reduction in renal blood-flow down to approximately a third of normal which was usually found (O Munck) could not be the cause of the persistent anuria. Munck also pointed out that there is at the moment no evidence as to what takes place during the initial phase of acute renal failure, and that, though it seems reasonable to suppose that there is usually an intense renal vasoconstriction, no measurements have been made at this time. There was a brief discussion of treatment by dialysis, under the chairmanship of J P Merrill. It was agreed that it was better for the patient to be dialysed at short intervals P E. Teschan dialyses every day but avoids repeated cut-downs by inserting plastic cannulæ into the radial artery and forearm vein which he leaves in situ until the end of treatment. B H. Scribner dialyses continuously throughout the twenty-four hours It was also agreed that it is better not to heparinise the patient but instead to heparinise the blood as it enters the dialyser and then to give protamine to the blood as it leaves the dialyser There was much discussion and no agreement as to whether cases of chronic renal failure should be dialysed C **BRUN** and J P **MERRILL** thought it unwise, whereas N **ALWALL** did not think that a generalisation was possible Finally, those at present in charge of dialysing centres thought that their number should be limited, preferably to the number at present in existence Surprisingly, the well-known objections to this recurrent ladder-lifting syndrome were not voiced.

Renal Transplantation

In this exciting session J P **MERRILL** and J **HAMBURGER** described the successful transplantation of kidneys from donors to recipients who were not identical twins Both speakers described how they first irradiated the recipients with approximately 450r from a cobalt bomb, to depress immunological processes Hamburger then placed the patient in a bacteria-free room, and the transplantation was performed under hypothermia on the day after the end of the irradiation Merrill had one patient alive after a year with good renal function and no proteinuria, though six months after the operation proteinuria had begun to appear This ceased after a further course of irradiation Hamburger had had two successful cases, one for one year and the other for six months, the latter a girl of 21 had recently married The transplant was most likely to be successful if the donor was a close relative of the recipient Later P P **LAMBERT**, and R **KUSS**, M **LEGRAIN**, and G **MATHÉ** described other cases

Other Topics

R L **VERNIER** demonstrated that the glomerular foot processes of dogs will become smudged after the intravenous administration of dog serum-protein, if it is given in such amounts that proteinuria is induced The foot pro returned to normal when protein administration was discontinued. This is a fairly convincing demonstration that smudging of the foot processes in the nephrotic syndrome is probably secondary to the proteinuria

T D **ULLMAN** showed that the antidiuretic effect of vasopressin during water diuresis was influenced by the pH of the urine and that during the formation of an alkaline urine there was relative insensitivity to exogenous vasopressin. It was pointed out that though there is as yet no explanation for this unexpected finding it is in line with Nutbourne and de Wardener's observation that hydrogen-ion excretion is depressed by a water diuresis

Finally, there was Y J **KATZ** and R S **MOORE**'s demonstration that the increase in white-cell excretion which follows the intravenous injection of a pyrogen in chronic pyelonephritis (Pears and Houghton) can also be obtained by the intravenous administration of 20 mg of prednisone phosphate

An International Association

During the congress it was decided to form an International Association of those interested in the kidney, and Prof J **HAMBURGER** was unanimously elected its first president It was proposed that there should be another international congress in three years, and an invitation from Dr Jan Brod to come to Prague was accepted.

H E DE WARDENER

CLINICAL ENZYMOLOGY

The 6th International Congress of Internal Medicine, held at Basle on Aug 24–27, included a day devoted to Enzyme Regulations in the Clinic

H **THEORELL** (Stockholm) surveyed the various modes of enzyme action, taking catalases, cytochromes, and dehydrogenases as typical examples It was important to elucidate the exact mode of action of an enzyme before using it as an analytical tool When this had been done, then enzyme measurements were as accurate as any other microchemical technique

C H **GRAY** (London) discussed the difficulties of measuring enzymes in body-fluids The ability to read a galvanometer needle with an error of less than 0 1% did not mean that the final calculated result had the same accuracy Clinical enzymology often produced results of relative significance only, and in the congenital abnormalities there was need for absolute values

The relation between genes and enzymes was reviewed by E **HADORN** (Zurich), who discussed the "one gene—one enzyme" hypothesis and the possibility that a single gene may control several enzymes or an enzyme with multiple functions

The functions and metabolism of organic phosphate compounds in heart-muscle were described by A **FLECKENSTEIN** (Freiburg), and R L **BING** (St Louis) gave a stimulating account of enzyme changes in cardiac metabolism The heart contained enzyme systems capable of utilising all the foodstuffs circulating in the blood but appeared to preferentially catabolise esterified fatty acids, particularly esters of oleic acid Studies on cardiac biopsy samples in the dog showed that tachycardia and ventricular fibrillation resulted in temporary increase in active phosphorylase together with accumulation of lactic acid

J V **TAGGART** (New York) considered the role of enzymes in renal metabolism, particularly with respect to the transport of substances across the tubular epithelium The exact location of the various enzymes in different segments of the nephron and the identification of the components of the transport mechanisms were the most challenging problems in current research

L **VILLA** (Milan) classified hepatic enzymes as primary, secondary, and accessory C J **WATSON** (Minneapolis) described bilirubin metabolism and discussed in detail the extrahepatic conjugation of bilirubin Even the severely damaged liver could both conjugate bilirubin and synthesise dihydroxy bile acids M J H **SMITH** (London) reviewed the use of blood-enzyme determinations in liver disease and concluded that it was not possible to distinguish specific patterns of blood-enzyme abnormalities for each hepatic disorder But serial estimations of transaminases and of other enzyme activities could give valuable help both in the diagnosis and in the assessment of the course and prognosis of particular liver diseases

The use of enzyme measurements in liver disease was discussed at length by a panel which included F **WROBLEWSKI** (New York), F **SCHMIDT** (Kassel), and D **ALLDIS** (London) The heterogeneity of serum enzymes, the misconception that necrosis of the liver accounts for raised blood-enzyme activities and the significance of serum-alkaline-phosphatase activities provoked vigorous debate

A. **VANNOTTI** (Lausanne) dealt with the enzymes present in the various cellular elements of the blood and with the effects of inflammation and hormone treatments on the enzyme patterns in leucocytes

J B **STANBURY** (Boston) distinguished five types of congenital hypothyroidism as inherited enzyme defects concerned with different stages in either the synthesis or the metabolism of the thyroid hormone One of these syndromes—that caused by a deficiency of a dehalogenase enzyme—was described in detail by A **QUERIDO** (Leiden) The primary defect appeared to be inability to dehalogenate iodotyrosine compounds which led to increased urinary excretion of organically bound iodine and lack of inorganic iodine for recirculation and incorporation into thyroglobulin The ultimate effect was a conditioned iodine deficiency causing decreased thyroxine synthesis

The discussions on clinical enzymology are to be published as a separate volume of the Congress proceedings

In England Now

A Running Commentary by Peripatetic Correspondents

NE view of members of hospital boards of management is t they are high-minded men and women, fired with husiasm for the public weal and anxious to sacrifice time and ure for suffering humanity Another is that they are an chosen collection of long-winded ninnies who would find ficulty in organising a game of ludo My own attitude bears elation to the date of the last board meeting and how fresh my mind is the dissertation by Baillie MacSpittle on the omparable superiority of wax polish over synthetic for the ing-room floor (his homily being interrupted by Lady ebell's reminiscences of the ballroom at the Hall in her her's time, the demands of Mr Smithkins, M.B.E., trade ionist, for enlightenment on the demarcation dispute between tron and Secretary, and General Roderick Philabeg's tention that all that is needed is *damned* elbow-grease), le my cherished and logically presented plan for the gently needed treatment-room is dismissed out of hand. I pose the truth lies somewhere between the two extremes t at board meetings I often find myself repeating under my eath the well-known remark that a camel is a horse planned a committee.

* * *

A short time ago, somewhat unwillingly, I accepted sound vice to undergo a major surgical procedure

I was admitted to an extremely pleasant single room, mplete with wireless and television, in a well-known women's spital. From this moment I was regarded as potential edical dynamite Not only was I a woman doctor, but I was o married to a doctor and all felt that the most unusual mplications were likely to develop The time of my operation as delayed so that ample blood should be available as my emoglobin was found to be low In fact, from my point of ew the operation and anæsthetic could not have been more erfect. The postoperative period passed in a delicious haze pethidine with remarkably little discomfort. I was quickly obile and felt incredibly fit. The time came for the removal my clips by the surgeon himself The result was a stunningly autiful scar, sister was in raptures The final accolade came hen the house-surgeon diffidently asked if he might view the asterpiece as its fame had spread. Nevertheless sister was leased to see me go She admonished me before her day off ot to do anything rash—she felt her good luck could not last nd there was an audible sigh of relief all round when on the elfth day I successfully took myself home

For my part I enjoyed my surgical experience far more than thought possible and was extremely happy except for one ing, the hardness of the mattress It was gorgeous to go to ed at home and relax in comfort Why, I wonder, do hard air mattresses still linger in modern hospitals?

* * *

Probably not many of us bother ourselves with such erstwhile issues as whether a viscount's half-brother should recede into dinner a duke's cousin once removed. What oes matter, however, are the problems of etiquette which ise on the London Underground

The lift presents no great problems, it is commonplace that he lady goes ahead of gentlemen—tradition demands it and here is the further point that the man is better placed to prise he wandering stiletto heel from the groove in which the gates un. And, of course, the man must take the risk of premature closure and entrapment Then he must remove his hat, put out his cigarette, and protect the lady from asphyxiation as far as possible Escalators are trickier Notwithstanding the igh-heel hazard, he should go first on the way down, providing a "soft-landing" as it were, and for the same reason second on the way up The extent to which one should conduct oneself thus with regard to *all* ladies, apart from one's travelling companions, is open to question. Strict observance of etiquette is likely to prolong travelling-time unduly, and might even be misconstrued.

Purchase of the tickets presents no special difficulties, but entry to the train is another matter, and this depends entirely on population density The gentleman must judge the ease with which entry to a crowded train may be forced and go in first if necessary with his umbrella so as to prise open a space of sufficient size. Two can seldom walk side by side down the passages—and here we must be *quite* firm. The lady must *always* go first, even though by following the green light for Victoria she may inadvertently land you at London Bridge

* * *

I seem to remember that, some years ago, Dickson Wright described the National Health Service as wailing and nationalisation of teeth. Is bruxism an occupational disease of medical practitioners?

* * *

The professional doctor's friend opens her attack subtly "We are looking for a doctor with young children himself," she says as the voices of my three children invade the wire from the upstairs extension. "Yours sounds a family home" The professional touch develops later "We were such good friends with our previous doctor—he almost lived at our house—I remember one Christmas Eve—he used to stay for hours—he was marvellous with the children—the weekend Aunt Sara came we called him three times—he never minded—we're hopeless about the surgery—I always seemed to be ringing his home at half-past ten." She and her family are most likeable folk and the propaganda works Two late evening calls and I find myself thinking, "Why can't I be their best friend like Harvey Doolittle? How could he do it? Did he enjoy the situation, had he no real friends, or had he, like me, tried too hard and succeeded?" "I don't understand these people always sending for a doctor, it's different among friends, otherwise I wouldn't dream of sending till we were desperate—except with children." Desperately I look round for fresh interests Harvey seemed to be a Leonardo He was marvellous with old wireless sets, he founded a boys' club, he was a churchwarden Alas, my glaring defects do not count against me, for I am a collector's piece, indispensable to the smooth running of their home Soon they are embossed in the visiting-list like their address on my prescription pad. At last they move on Their new home is conveniently near the new surgery "We are sure we are going to like him"

* * *

East-West trade note—We took our eleven-year-old to hear the Leningrad Symphony Orchestra. He disappeared during the interval and came back without his tie (a hunting Stuart tartan) He had exchanged it for two Sputnik badges, a 20-kopek piece, 10 autographs, and, thrown in, a kiss from the trumpeter

* * *

SE TAIRE C'EST PLAIRE

Among the rarest
(Seamus said)
Of all the family joules
Was formerly a hard-boiled erg
And on its sleek and shining shell
Was writ "O Man!
Think'st thou
T'evade the circumambient here and now?
Dost dream
Of some seductive but fallacious scheme—
Of some eternal effort-saving notion?
No! Accept the yoke
Be meek
Fall not into temptation
Do not seek
Perpetual motion but perpetual motivation!"
Well
Of course the thing is sold
But it was pretty to behold.

Letters to the Editor

ONE FORCES' MEDICAL SERVICE ?

SIR,—The fact that I was arrested as a spy on entering a British front-line trench on the Pilckem Ridge in the first world war does not deter me from leaving the underground council chamber of the British Medical Association to make a sortie into what I suspect from reading your annotation of Aug 13 to be a somewhat hastily prepared position

You note (with glee?) that the Select Committee on Estimates in their fourth report criticised the Service Departments as "disappointingly inflexible" and consider that the latest observations of the Ministers concerned "will do little to alter the Committee's view", implying that any "stagnation of trench conflict" which may ensue will primarily be due to the Service departments and the Ministry of Defence

But you do not note, as did the B M A council with the advice of its Armed Forces Committee, any of the following significant points regarding the findings of the Select Committee

1 That the main recommendation for integration was not supported by the weight of evidence Nearly all the evidence given to it from all sources—independent and civilian as well as Service and official—was either against it or did not support it

The conclusion upon which it was based—"The objections to integration formulated by the Waverley Committee have in large part been weakened or invalidated by subsequent events, and the inauguration of the Canadian scheme"—was unsound The only changes we know of are those beneficial ones which have followed the adoption of some of the Waverley Committee's recommendations The only witness heard by the Select Committee who was also a member of the Waverley Committee was Sir Arthur Porritt He stated in evidence "I think—and I still feel as I did then, perhaps even more so—that it would be a great pity from a recruitment point of view, from the medical angle, that they should be amalgamated", and, again "I believe most of the things we want to achieve can be effected by increased co-ordination and not amalgamation, considering the traditions behind the Services"

2 The Mond Weir Committee in 1923, the Government in 1946–48, and the Waverley Committee in 1955 considered that integration would be unlikely to show substantial economies or increased efficiency, and would be likely to affect adversely medical recruitment

No evidence is given of any economies or of greater efficiency which would arise from integration, nor does the Select Committee specify how these things will be obtained

It is not surprising, of course, that no evidence was given of these things resulting from the Canadian scheme, because that was inaugurated only 12 days before the Select Committee began to hear evidence[1]

3 There appears no justification on present evidence for throwing aside our traditional freedom of choice for young doctors to make a career in a Service to which they feel particularly attracted

In the incident referred to in the first paragraph, I was sent back to battalion headquarters between fixed bayonets and given lunch in the mess as part of a test Should you wish to test any of the above points, I should be happy to submit in a similar way in your headquarters

REGINALD STANBRIDGE

Oxshott, Surrey — Chairman, Armed Forces Committee, B M A

*** After the late war, we were demanding integration [1] with as much vigour as Air Vice-Marshal Stanbridge opposes it Our comment on the Select Committee's report did justice to the objections,[2] but we still w see the Services brought closer together —ED L

ORNITHOSIS AND RAILWAY GUARDS

SIR,—The editor of the *Racing Pigeon* has now asked (July 16, Aug 27) for evidence of infections in humans resulting from racing-pigeons

In 1948 we found evidence of ornithosis infection in t family of a pigeon-fancier, and we started serological tions of racing-pigeons and other domestic pigeons Soon found a high percentage of serologically positive reactions ornithosis antigen in racing-pigeons and a low positive reactions in any other type of domestic Subsequently, Winsser [3] isolated the virus from pigeons wh had been a source of infection We have since examined than two thousand serum samples of pigeons and never group of racing-pigeons in which less than 30% showed logical evidence of infection, from many of these pigeons isolation was relatively easy We did find some groups pigeons without evidence of infection, but none of these racing-pigeons

It should be emphasised that ornithosis virus has a very pathogenicity for pigeons, and that birds which are ap in a very healthy condition excrete this virus and are sequently infective to their fellow-travellers in railway va to their caretakers there, and to their owner and his family home As racing-pigeons frequently travel together, som times for days, in a relatively small space, it is obvious that f of them could hope to escape infection

The infectivity and virulence of this pigeon-ornithos virus for man are also very low although most pigeon-fancie have positive complement-fixation tests with ornithosis antige some of them may have negative reactions even if their loft heavily infected and virus is readily isolated from the bird Of 843 ornithosis patients diagnosed in the Netherlands sin 1948, 270 had had contact with pigeons (mainly racin pigeons), only 80 of these were women

Since 1950 clinicians in this country have been increas-ingly aware of the possibility of ornithosis in cases c atypical pneumonia, and now 4000–5000 serum sampl from these patients are examined annually, we feel th perhaps half the patients seriously ill with ornithos with pigeons as the source of infection are diagnose as such, the annual average is about 25 As there are abo three hundred thousand organised racing-pigeon fanciers in the Netherlands, the risk of infection is obviousl very small This risk should therefore not be exaggerated, but it is impossible to deny it as Mr Osman does Furthermore, there is an obvious difference between racing-pigeons and other domestic pigeons in that the former are certainly more heavily infected than the latter I think that any British virologist who would care to examine the serum of racing-pigeons for evidence o ornithosis infection would get the same results we did

Central Institute for Ornithosis Research of the
Netherlands Public Health Service, Amsterdam — F DEKKING

UNITS

SIR,—Dr Eaton's plea last week for uniformity in the use of units reminds me of a lecture on corrosion by the late Dr W E Gibbs, Ramsay professor of chemical engineering at University College, London Quotin corrosion-rates expressed in milligrammes per square foot per day, Professor Gibbs added "I apologise, gentlemen, for these bastard units But what else can one expect from the union of chemistry with engineering?"

F H BELL

Newcastle upon Tyne.

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[1] *Lancet*, 1946, ii, 421, 523, 1947, i, 373, 1947, ii, 799

[2] *ibid* 1959, ii, 336

[3] Winsser, J, Dekking, F, en Stol, H J *Tijdschr Diergeneesk*, 194 74, 423,

OUR POOR THAMES

R,—Dr Mackenzie-Wintle writes in your issue of 10 "I have spoken to many doctors, but I have yet nd one who can quote me a single case of typhoid, omyelitis, or even Weil's disease which could reason- be presumed to have its origin in the ingestion of water"

he means by this that leptospirosis is not contracted ngestion he may well be right, but if he intends to ly that the Thames water does not convey the infec- then I believe him to be quite mistaken In the past years I have had at least a score of cases in men and s following bathing or fishing in the river or its utaries Most cases were mild—far removed from usual textbook descriptions—and might well have ped detection had the condition not been suspected, the appropriate investigations carried out

ertainly in this part of the Thames Valley leptospirosis t be seriously considered in the differential diagnosis hepatitis and/or meningitis Renal lesions, while ent, are rarely obtrusive.

th Middlesex Hospital,
Isleworth.

G E BREEN

IR,—It is without surprise that we learn from Mr il Jarvis (Sept. 3) and Dr Mackenzie-Wintle that the ames is heavily polluted with fæces much nearer to source than Staines

r Mackenzie-Wintle's advice that "the healthful cts of [river] bathing very far outweigh any risk olved" we feel is an astonishing statement to come m anyone having specialised knowledge of waterborne eases A little over a hundred years ago critics of Snow must have made similar statements when he nted out that the cholera epidemic that raged in Soho s associated with water from the Broad Street pump

We would like to point out that all or practically all hers swallow some water while swimming, many allow a considerable volume We are certain that no dical officer of health would ever regard untreated ames water as bacteriologically safe to drink, and since imming involves drinking it must follow that the river ter is equally dangerous to bathe in.

and-Seaton Institute of Pathology,
Middlesex Hospital,
London W 1

R. E M THOMPSON
D B LONGMORE

TROLLEY-SETTING

SIR,—The provision of individual packs of dressings d instruments by central sterile supply departments akes it necessary and possible to modify the present actice of trolley-setting

Bowls and gallipots are a nuisance to sterilise and their use is rely traditional and quite unnecessary Dressings should be ed straight out of the pack and should not be emptied into a wl, and the use of gallipots for antiseptics and lotions can be ded equally easily There is no need to soak a swab in a llipot full of spirit in order to clean the skin before an injec- cn. A few drops delivered from a drop bottle on to the swab e equally effective. I do not advocate the use of sprays for s purpose, as I believe the mechanical rubbing action is more portant than the chemical action of the antiseptic applied for few seconds For preoperative skin preparations, however, spray is a most efficient instrument and will save swabs, tiseptics, gallipots, and time.

The pernicious custom of keeping fluids for injection in one f a row of unlabelled gallipots is now rarely seen, but one still ars of cases where spirit has been injected by mistake.

I believe there is no procedure which could not be improved y abandoning the use of bowls and gallipots, and their presence on a trolley is a sign of bad practice. Dressings should be used from individual packs, antiseptics from drop bottles or sprays, injections from ampoules or multi-dose containers—swabbed clean, not dipped into gallipots Water and saline should be dispensed in small sterile bottles, which are used once only, and dirty dressings should be discarded into dispensable paper bags, not into bowls

Can we persuade G N C examiners to share this view?

Central Pathological Laboratory,
Burnley, Lancs

G BEHR.

LOCAN PESSARIES IN THE TREATMENT OF TRICHOMONAL VAGINITIS

SIR,—The findings of Dr Eckersley and his colleagues (Sept. 3) accord with those in the Edinburgh special clinics

Some time ago Dr Murrell[1] referred to the number of cases in which local sensitivity to 'Locan' developed. In a further trial of the drug many patients complained of "intense vulvar heat", and examination showed either severe vulvar œdema or an urticarial rash. One of my patients, in addition to the vulvar symptoms, had a rash on the fingers used to insert the pessaries, these side-effects subsided with discontinuation of the pessaries This patient had no history of previous sensitivity to cocaine.

In view of these reactions, and because many other forms of local therapy are available, locan pessaries are not used in our clinics

Special Clinic,
Royal Infirmary, Edinburgh, 3

MARY SCOTT-GRAY

DOCTORS, ADMINISTRATORS, AND THERAPEUTIC COMMUNITIES

SIR,—The excellent article by Dr Crocket (Aug 13) does, as subsequent correspondents have observed, point the way to reforms long overdue. But first clarification of the position of medical superintendents under the new Mental Health Act, which comes into operation on Nov 1, is needed. To those who work in general hospitals it may seem incredible that the following points are still bones of contention

1 The right of individual consultants to attend to correspondence about their own patients From long usage letters are still often addressed to the medical superintendent and dealt with by him even though they concern another consultant's patients This applies to all correspondence but especially that on legal matters

2. The right of the consultant to know exactly which patients are under his charge. There are still spheres where some medical superintendents assume a sort of roving commission, especially in moving patients from ward to ward, "reviewing" them, and corresponding with their relatives

3 The right to an equal share of new cases where no particular consultant is requested. Here again through custom, requests for admission, consultation (domiciliary or in clinics), and examination of prisoners and court cases are often addressed to the medical superintendent and are not shared. to a mental hospital only through the medical superintendent. Some general practitioners still think they can admit a patient In other words what corresponds to periods "on take" in general hospitals, whereby all consultants have a share of such cases, does not exist in some mental hospitals

These are some of the basic problems which must be resolved if we are to put behind us the chronic dissatisfaction and frustration which has often existed in the past. There are, of course, many ways of doing this, among which are the following

1 Negotiation in individual mental hospitals—probably the worst method.

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[1] Murrell, M. *Lancet*, 1957, ii, 1235

2 Clear guidance from the Minister of Health

3 A small committee composed of medical superintendents and consultants to examine the problem and submit their findings to wider opinion such as regional meetings of those concerned This is the method I personally would favour

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Oxford

J E DUFFIELD

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—Dr Ahrenfeldt, in his letter last week, says that it is useless and also highly detrimental to the patient and society alike to make recommendations to a juvenile court which cannot in practice be implemented

I myself prepare reports which give what I believe the court has requested—namely, my advice as a psychiatrist about the action to be taken in a particular case If I find a child needing inpatient treatment I say so I know that the pitiful number of psychiatric beds for children in London makes it unlikely that the child can be admitted It is important that magistrates, probation officers, welfare workers, and officials should also discover this, so that pressure can be built up to remedy this state of affairs It may be that we shall have to make do with placement in a residential school for the maladjusted, but even then it is better that all concerned know that it is a second-best and that the child needs something more

Similarly, if I feel that an adult psychopath needs hospital treatment, I should say so I know that the chances of securing his admission to the place of choice (perhaps the Henderson Hospital) are small, but as a physician I must state my patients' needs, as I see them Failing to secure an admission, the court may have to decide to commit the person to prison, but it is surely important for them to see that what may be practical in social terms is not necessarily what is in the patient's interest

I believe that, so long as psychiatrists confine themselves to making recommendations which fall within the present totally inadequate facilities, so long will this state of affairs persist, to the detriment of the individual, and of the society which at present cannot or will not make provision for the care and treatment which we believe is required

London, S W 5

W H ALLCHIN

MYOCARDIAL INFARCTION DURING PREGNANCY AND PUERPERIUM

SIR,—I should like to comment on the interesting paper (Sept 3) by Dr Watson and his colleagues

As they observe, serious atheroma is uncommon in women of childbearing age, and the youth of their patients is particularly striking Thrombotic occlusion of a coronary artery is also rare in young pregnant women, and I believe that dissecting aneurysm should be considered as a possible cause of myocardial ischæmia in these cases

Dissecting aneurysms primarily involving systemic arteries other than the aorta are certainly unusual, but have been reported with increasing frequency in recent years In a report of 4 new cases in 1956, reference was made to only 15 acceptable cases in the earlier literature [1] Since then more than 30 further cases have been reported—no less than 17 of them in one recent paper [2]—and a few additional cases have been unearthed from the literature These various reports include a total of 9 well-documented cases with dissecting aneurysm of a coronary artery,[3-9] and it is notable that 2 of these were puerperal [6 8]

A definite association is known to exist between pregnancy and dissecting aneurysm of the aorta,[10] and it may be tha holds for the coronary arteries also The nature of apparent association is quite unknown although in cases stresses induced by the physical exertion of deliver be responsible, violent exertion was considered to be the of the 2 instances in soldiers reported by Uehlinger [4] In these cases to which I have referred the diagnosis was only at necropsy, but this reflects the difficulty of rather than the inevitability of a fatal issue Even at necrop is possible to mistake a dissecting aneurysm in a med sized or small artery for thrombotic occlusion on naked examination [1] It may be added that, in contrast to dissecting aneurysm, occlusion of the lumen is much common in these smaller vessels than external rupt Finally, the youth of the patients described by Watson et more easily reconciled with a diagnosis of dissecting aneu than with coronary atheroma and thrombosis

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A J WATSO

ACCURACY OF INJECTIONS FROM MULTIDOSE CONTAINERS

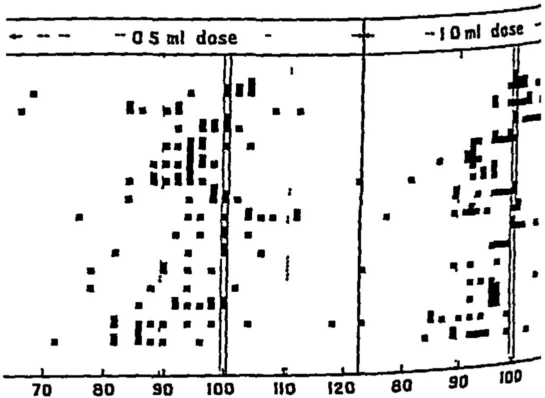
SIR,—The introduction of double-strength vaccin 0 5 ml doses increases the possibility that the error in volume administered may sometimes be ur great [11] To investigate this we invited 15 doctors in pu health work and general practice to inject altern 0 5 ml and 1 0 ml water from a multidose conta into a series of small rubber-capped vials, simulatin closely as possible their personal technique of inocula

120 injections of 0 5 ml nominal and 112 injectio 1 0 ml nominal were returned and were accurately meas by reaspiration into a syringe graduated in divisions of 0 0 This procedure was checked and found accurate to ±2%

The results are shown in the accompanying figure 13 4% of 1 0 ml doses and in 26 5% of 0 5 ml doses injected volume differs from the intended volume by more 10% (this range is quite arbitrary)

	0 5 ml	*1 0 ml*
Total injections	120	112
Total below 90% of volume intended	27	15
Total above 110% of volume intended	5	0
Error exceeds 10%	32 (26 5%)	15 (13

Although the difference is statistically significant ($P<0$ we do not want to exaggerate its importance In the first some doctors were much more accurate than others, and though all were regularly giving immunising injections, sample chosen may not have been representative. Secon with most childhood inoculations, it is not the present cu to make any allowance for age and size In fact, antigens as diphtheria and tetanus are probably sufficiently effe and well tolerated to permit wide dosage limits



Volume measured as percentage of volume intended he limits with certain other antigens, however, including ussis, are not so wide, and we think it is worth drawing ntion to the increased likelihood of inaccurate and most monly underdosage when smaller volumes are given in way It is desirable to use a 1 0 ml. syringe and to take icular care in measuring the volume There is an obvious ntage in using ampoules in which single doses have been rately measured by the manufacturer, although the cost is ter

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[1] Watson, A J *J Path Bact* 1956, 72, 439
[2] Foord, A G, Lewis, R D *Arch Path* 1960, 68, 533
[3] Glendy, R. E, Castleman, B, White, P D *Amer Heart J* 1937, 13, 129
[4] Uehlinger, E *Schweiz med Wschr* 1947, 77, 608
[5] Hedinger, G *Cardiologia*, 1947, 12, 46
[6] Lovitt, W V, Jr, Corzine, W J, Jr *Arch Path* 1952, 54, 458
[7] Ahronheim, J H, Wagman, G F *ibid* 1959, 67, 19
[8] Wells, A L *J Path Bact* 1960, 79, 404
[9] Boschetti, A E., Levine, A *Arch intern Med* 1958, 102, 562

[10] Schnitker, M A, Bayer, C A *Ann intern Med* 1944, 20, 45
[11] Burn, J L *Lancet*, 1960, i, 437

he majority of the doctors expressing a preference chose 0 5 ml. dose In a trial involving an individual follow-up of babies we were not, however, able to demonstrate any real erence between the two types of triple antigen, either in the nediate response or in the reaction-rate during the first ours

/e are grateful to our colleagues and to the health visitors who ted in the investigations

reenford, Middlesex. T B BINNS
ilford, Lancs J L BURN

CHROMOSOME ANALYSIS

IR,—The method of chromosome analysis described Bottura and Ferrari[1] and used by your contributors[2, 3] es not seem clinically justifiable since it involves the ministration of colchicine derivatives to patients

t is known that colchicine causes heteroploidy and tri- idy in animals, and its antimitotic properties are utilised in treatment of patients with leukæmia. Since leukæmia may associated with an abnormal karyotype there would seem be a risk of causing leukæmia in healthy subjects by the use antimitotic agents The incidence of leukæmia is higher in ngols, who are heteroploid, and it would therefore seem ecially hazardous to use antimitotics for diagnostic purposes patients of suspected abnormal karyotype

The intravenous administration of colchicine deriva- es for diagnosis is unnecessary and potentially dan- rous Their use for this purpose seems clinically acceptable and should be condemned

Department of Surgery,
Queen's College,
Dundee. JOHN S S STEWART

THE FEMALE PROSTATE

SIR,—When Mr Moore published his article[4] I was uite impressed as I had worked on the same subject hen I read Mr Skyrme Rees' letter (July 9) I was uite surprised that he denies the existence of periurethral ands (female prostate) in general

When he states that prostatic carcinoma in the female is nknown in the animal kingdom, he is partially at fault. There e enough cases of carcinoma of the periurethral glands, hich are the homologue of the male prostate I was able to llect 41 reported cases with significant clinical and patho- gical data and added 3 cases of my own[5] The literature n the embryology, anatomy, histology, and physiology of ese glands is quite extensive and the fact that they exist as been well established They respond to androgens in the ame fashion as the male prostate Mr Moore, in his reply July 23) to Mr Rees' letter, says that it is not surprising that arcinomas of the female prostate do not occur because of the igh œstrogenic environment

I would like to point out that in analysing the literature found that, of 44 collected cases, only 2 had occurred before he 5th decade Therefore I concluded that adenocarcinoma f the female urethra (female prostate) is almost exclusively disease of menopausal or postmenopausal women It is uite possible that the high œstrogenic environment before he menopausal period does not permit the development of a carcinoma of the female prostate During the menopause and after, when the œstrogen level falls rapidly and when the female prostate could respond to androgens from the adrenal glands, it is possible that an occasional carcinoma develops in these glands

The carcinoma of the female prostate undoubtedly exists, though it is very rare In my short practice of pathology, I was able to observe 4 such cases

Wayne County General Hospital,
Eloise, Michigan, U S A ROMAN KNOBLICH

Bottura, C., Ferrari, I *Nature, Lond* 1960 186, 904.
De Assis, L. M, Epps D R., Bottura, C. *Lancet*, July 16 1960, p 129
Leon, N, Ferrari, I, Bottura, C. *ibid* Aug 6, 1960, p 319
Moore T *Lancet*, 1960, i, 1305
Amer J Obstet Gynec 1960, 80, 353

CATECHOLAMINE METABOLISM IN NEUROBLASTOMAS

SIR,—Study of catecholamine metabolism in association with phæochromocytomas has been extensive These findings have proved most beneficial in diagnosis and follow-up care of such patients However, few studies have been published regarding urinary excretion of noradrenaline, adrenaline, and 3-methoxy-4-hydroxy-mandelic acid (V M A) in an embryologically related neural tumour, the neuroblastoma

In 1957 Mason et al[1] first reported increased urinary excretion of pressor amines in an infant with a neuroblastoma Isaacs et al.,[2] Graham,[3] Stickler et al.,[4] and von Studnitz[5] have since recorded additional cases Another possible case is referred to by Wilkins[6]

Five infants and children with a tissue diagnosis of neuroblastoma have been investigated in our laboratory Therapy in these patients consisted of surgery, intravenous nitrogen mustard, and/or radiation Urinary excretion of noradrenaline and adrenaline was determined according to the method of von Euler and Floding[7] Urinary V M.A was estimated using the method of Armstrong et al[8]

Urinary Excretion in µg per 24 hours

Patient	*Age*	*Before treatment*		*After treatment*	*Exacerbation*	*Normal value*
1	5½ yr	Noradrenaline	53 7	15 3	69·6	<25
		V.M.A.	3625 0	2745 0	12,600 0	<2000
2	13 mos	Noradrenaline	104 4	7 3		<15
		V.M.A.	1525·0	570 0		<1000
3	4 yr	Noradrenaline	121·5	63·0	105·0	<25
		V.M.A.	1752·0	1100 0	1360·0	<2000
4	7 mos	Noradrenaline		3 1	12 3	<15
		V.M.A.		500 0	690·0	<1000
5	7 wk	Noradrenaline	14 7		13·4	<10
		V.M.A.	8000·0		28,750 0	<500

In patients 1 and 2 we found increased amounts of noradrenaline and V.M.A. before treatment. After treatment, the patients improved, and the values of these substances decreased When patient 1 had exacerbation of his disease, the urinary excretion of noradrenaline and V M.A. again increased. Patient 3 had increased excretion of noradrenaline before therapy, a clinical remission and decreased noradrenaline excretion after treatment, and increased noradrenaline excretion when the disease progressed V M.A. excretion remained normal throughout this time Patient 4, who had severe generalised disease, excreted normal amounts of noradrenaline and V.M.A. in her urine during the course of her illness Little or no benefit was derived from therapy, and the patient died within three months Patient 5 had a slightly raised urinary noradrenaline, but a much elevated excretion of V.M.A. He, too, responded poorly to therapy and died within three weeks

Urinary adrenaline was within the normal range in all cases

These findings suggest that there is wide variation in the biochemical nature of these tumours Alternate pathways for synthesis and metabolism of noradrenaline and adrenaline may be present. Serial determinations of the catecholamines and their metabolites seem to have

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1 Mason, G A Hart-Mercer, J, Millar, E J, Strang, L. B, Wynne, N A. *Lancet*, 1957, ii, 322.
2. Isaacs, H Medalie, M, Politzer, W M *Brit med. J* 1959, i, 401
3 Graham, J D P *Nature, Lond.* 1959 183, 1734
4 Stickler, G B, Hallenbeck, G A., Flock, E V *Proc Mayo Clin.* 1959, 34, 548
5 von Studnitz, W *Scand. J clin. Lab Invest* 1960, 12, suppl. 48, p 53
6 Wilkins, L. The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence Springfield, Ill., 1957
7 von Euler, U S, Floding I *Scand. J clin Lab Invest* 1956, 8, 288
8 Armstrong M. D., McMillan, A., Shaw, K. N F *Biochim. biophys. acta*, 1957, 25, 422.

prognostic implications and to be useful in evaluating response to therapy Studies of patients with neuroblastomas may permit a biochemical classification of these tumours in the near future

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State University of New York,
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MARY L VOORHESS
LYTT I GARDNER

PULSE-GIVING PUMP

SIR,—Your issue of April 30 contained an account of a new pulse-giving pump [1]

I constructed a pump on this principle in 1948, and exhibited a working model at a combined meeting of the British Medical Association and the physiology department of the University of Melbourne in July, 1951 The project was discontinued owing to lack of financial support I did, however, publish the essential principle of external compression by a piston [2] Air was used instead of fluid as a compression medium, owing to constructional difficulties in a home-made device

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R F BUTTERWORTH

ZOLLINGER-ELLISON SYNDROME

SIR,—Our experience with case 2 of Verner and Morrison [3] leads us to agree that this syndrome indeed has many facets

We observed this patient from the onset of his symptoms until his death 804 days later and are still groping toward a solution of the mystery of his disease We were most struck by the prolonged abnormality of calcium metabolism, which was characterised by hypercalcæmia, hypophosphatæmia, and hypercalciuria 33 serum-calcium determinations were made and of these 20 were greater than 10 5 mg per 100 ml, the greatest being 16 5 mg Before neck exploration, hypercalciuria was consistently present, daily urinary calciums being 469, 390, 382, and 320 mg Following exploration on the 155th day after onset there was a marked decrease in calcium excretion except for the first postoperative day when 247 mg was excreted Thereafter the maximum obtained was 215 mg on the 256th day, random 24-hour urine-calciums were 89, 124, 3, 23, 12, 27, 78, 11, 163, 155, 47, 40, 82, and 86 mg On three separate occasions (days 224, 322, and 347) hypercalcæmia was accompanied by hyperphosphatæmia, azotæmia, and a decreased carbon-dioxide combining power Serum-potassium was less than 3 5 mEq per litre on 32 occasions, was normal 4 times, and was greater than 5 mEq per litre only once Despite the prolonged hypokalæmia the carbon-dioxide combining power was elevated (36 mEq per litre) only once and was less than normal on 18 of 23 determinations Partial balance study was done between days 632 and 638, and data relative to potassium intake and urinary excretion were as follows

Day	*Diet*	*Intake (mEq) supplement*	*Total*	*Urinary excretion (mEq per litre)*	*Urine volume (litres)*
1	107	205	312	20 8	2 2
2	212	205	417	25 7	3 5
3	146	205	351	35 1	3 3
4	143	205	348	29 9	2 6
5	163	205	368	36 9	2 6
6	143	205	348	37 8	2 3
Total	914	1230	2144	186 2	

During the study diarrhœa was not a problem, and 3 of the 4 normal serum-potassium values obtained were within three weeks of the study Potassium balance cannot be absolute because fæcal collections were not made, but serum-potassium at the beginning of the study was 2 mEq per litre and twenty days later was 4 8 mEq per litre Serum-calcium at this time was normal

These observations suggest an intermittently active tumour, but the mechanism by which changes were effected is The three episodes of hypercalcæmia, hyperpho and azotæmia suggest that the tumour may have elabor vitamin-D-like material which may have accelerated absorption of calcium from the bowel, not unlike the mech thought to account for the hypercalcæmia of sarcoid The relation of hypercalcæmia to hypokalæmia is lik unclear, although it has been demonstrated by stop techniques that calcium infusion in dogs leads to urinary excretion of potassium [4,5] Epstein [6] has also hypercalcæmia as a possible factor in producing in man, probably by its action on the distal nephron. relative to calcium loading in humans are inconclusive, calcium loading is rarely extended beyond eight hours. absence of extensive renal calcification at necropsy possibly can be accounted for by the intermittency of hy calcæmia, the presence of the typical lesions of kalicpe nephropathy at necropsy does not exclude the role of calc Epstein et al [7] in fact have demonstrated similar lesio rats made hypercalcæmic by calciferol We have rec observed hypokalæmia with hypercalcæmia in a patient hyperparathyroidism due to hyperplasia and in another multiple myeloma Parathyroidectomy restored these valu normal in the first case while cortisone was effective in second

We have also observed another patient with hypercalc and lymphosarcoma who on one occasion also had hyp phosphatæmia and azotæmia (blood-urea-nitrogen 88 mg p 100 ml) This patient, a middle-aged woman, had previo undergone nephrectomy because of pyelonephritis assoc with cystinuria and stone formation She was adm initially because of unexplained fever and splenomegaly initial daily urinary calcium excretions were 123, 114, 118 mg She was given sodium phytate and a low calc diet with a fall in her serum-calcium from 14 2 to 9 9 calcium excretion values during this period were 78, 56, 3 and 58 mg per day After this therapy was stopped she on day excreted 376 mg calcium Splenectomy was then p formed and lymphosarcoma demonstrated Her ser calcium fell from 13 6 preoperatively to 11 5 mg per 100 and her urinary calcium excretion to about 200 mg d However, with recurrence of her tumour, calcium excre increased and reached 302 mg on one occasion shortly be her death These findings suggest that the tumour may h secreted a vitamin-D-like material and that such activity partially counteracted by the action of sodium phytate.

This study was supported in part by a grant from the Nat Institutes of Health, Bethesda, Maryland

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Winston Salem,
North Carolina

JOHN H FELTS
WILLIAM H BOYCE
ROBERT W PRICHARD

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—Dr Stephen Carter (Aug 13) rightly ca attention to the great waste of time in sterilisation of th diabetic's syringe One might also mention the proble of the diabetic when travelling away from home

The recent availability of sterile disposable syringes wi attached needles at a cost of less than 15 cents (U S A) ea (in 2 ml sizes) has led me to supply some to diabetic patien with instructions that immediately after injections they plu the needle back into the rubber vial cap and store the syrin needle-vial assembly thus, preferably in a refrigerator, un the next usage, discarding the syringe only when the vial empty

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SAM I LERMAN

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[1] Sorensen, A H *Lancet*, 1960, i, 959
[2] Butterworth, R F *J thorac Surg* 1951, 22, 316
[3] Verner, J V, Morrison A, B *Amer J Med* 1958, 25, 374
[4] Henneman, P H, Dempsey, E F, Carroll, E L, Albright, F *J* *Invest* 1956, 35, 1229
[5] Howard, P J, Wilde, W S, Malvin, R L *Amer J Physiol* 19 197, 337 Samiy, A H E, Brown, J L, Globus, D L *ibid* 19 198, 59
[6] Ferris, T F, Levitin, H, Epstein, F H *J clin Invest* 1960, 39,
[7] Epstein, F H, Rivera, M J, Carone, F A *ibid* 1958, 37, 1702

ARTIFICIAL INSEMINATION

IR,—Concupiscence was necessarily part and parcel of ltery before the advent of A I D With A I D, however, question of concupiscence (defined as ' lust ") does arise In reply to Dr L N Jackson (Aug 27), I not do better than quote from John P Kenny, O P

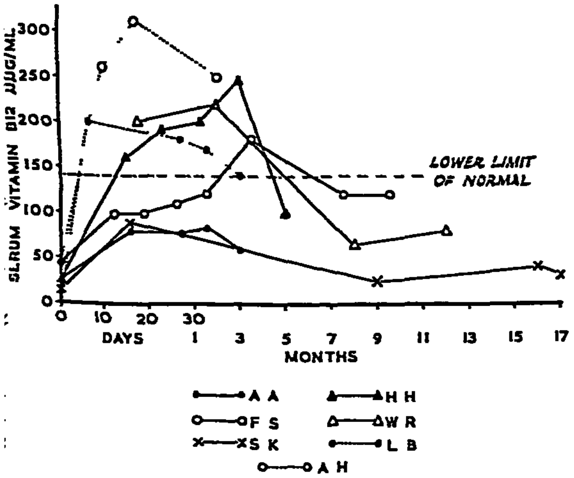
The nature of the marital contract precludes a woman from iving any seed except that of her husband. The right to pagate children is received in virtue of the marriage tract This right belongs to husband and wife, and cannot transferred to or used by a third party If marriage rights e transferable, it would imply that the marriage bond itself ommunicable "[1]

ale, Cheshire. A. F ROBERTS

RAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P.P /1

SIR,—Dr Mooney and Dr Heathcote (Aug 6) draw conclusion that their vitamin-B_{12}-peptide complex is re potent in the oral treatment of pernicious anæmia n the equivalent amount of crystalline vitamin B_{12} fortunately their observations do not decide whether s form of therapy is a good one

We have investigated 10 patients treated with 'Distivit' eir peptide-vitamin-B_{12} complex) The accompanying ure shows the serum-vitamin-B_{12} levels of 7 patients thus



ated, in 3 the investigations were not complete. Assays were ne by the *Euglena gracilis* var bacillaris method of Ross The ses used were one 100 μg tablet t.d. for ten days, followed one 100 μg tablet once a day in case S K the dosage was duced to 20 μg once a day after the first four months of eatment. The hæmatological responses, although slower than ter parenteral treatment, were as a whole satisfactory 1 of e patients, however, relapsed on 100 μg daily maintenance se, and the patient on 20 μg doses in addition developed gns of subacute combined degeneration

In 2 patients (A A and S K.) the vitamin-B_{12} serum levels mained throughout pathological in spite of a hæmatological nprovement, and in most of the others the levels decreased subnormal or low values after three to eleven months of aintenance therapy

It is absolutely essential to do serial vitamin-B_{12} serum timations in all patients treated orally, say, every three onths, whatever the form of oral preparation used (intrinsic ctor – B_{12} or B_{12}-peptide complex), because the amount of tamin B_{12} absorbed from the small gut appears to vary from se to case Also it seems that after either type of oral preparaon there may be some degree of inability to absorb satisctory amounts of the vitamin

Until such time as a safe commercial oral preparation, guaranteeing a satisfactory absorption of B_{12}, becomes available, oral B_{12} preparations should not be used in the treatment of pernicious anæmia If, for some reason or other, oral treatment is preferred for *maintenance* therapy, periodic, say three-monthly, checks of the serum B_{12} level should be carried out.

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S VARADI
A ELWIS

2-DIMETHYLAMINOETHANOL BITARTRATE (ATROL) IN DEPRESSIVE ILLNESSES AND CHRONIC SCHIZOPHRENIA

SIR,—The anti-depressive effects of 2-dimethylaminoethanol (deanol) bitartrate (' Atrol ') have been studied in 45 patients, 20 of whom had depressive illnesses and 25 chronic schizophrenia This letter gives an account of a clinical impression without the use of controls, and the dosage and duration of treatment were determined by day-to-day clinical progress

Depressive Illnesses

The 20 patients with depressive illnesses were classified as follows endogenous (including involutional) 13, manic depressive 1, neurotic depressive reaction 4, secondary to dementia 2 In the endogenous group none became worse, 9 were unchanged, 3 were slightly improved, and 1 showed a very good result.

Of the 9 endogenous depressives who were unchanged by treatment with atrol, all were severely ill, 5 were psychotic, and 3 were of long duration. The maximum daily doses which these 9 patients received were 40 mg (1), 60 mg (1), 100 mg (1), 120 mg (3), 200 mg (2), 400 mg (1) (the only patient to whom the tablets were given in divided dosage, and only when the dose was raised above 200 mg in one day)

Of the 3 who showed slight improvement, 1 had a maximum of 60 mg daily and his improvement is only just being maintained with 20 mg daily without maintenance electroconvulsive therapy (E.C.T) The second, a chronic elderly depressive, is brighter and less generally retarded, and is being maintained on 100 mg daily The third is a man with a mixed depressive and paranoid psychosis, in whom the depressive component is alleviated by 200 mg daily

The very good result was in an elderly man with chronic depression who had been in hospital for thirty-three years, he improved markedly on 80 mg per day, and is now being maintained on 40 mg per day

The manic-depressive patient was on the verge of depressive stupor, and his condition failed to respond to 200 mg daily he required E C T for relief

1 of the 4 people with neurotic depressive reactions showed a very good result, 2 were slightly improved, and 1 was unchanged I am reluctant to attribute unreservedly these three improvements to the drug because of other factors

A lady with severe dementia and a secondary retarded depression, when given 40 mg daily, absconded from the ward, and on being brought back was belligerently resistive, until the effect wore off in two or three days The second patient with depression secondary to dementia was unchanged.

No unwanted clinical side-effects occurred, and it is of interest that a man of 83 who was given 400 mg daily without over-stimulation had previously been in what one can call a pre-convulsive state of hyper-reactivity from a normally therapeutic dosage of imipramine[1]

My impression is that this drug is of little benefit in the treatment of severe endogenous depressions especially those with agitation, a viewpoint which is shared by Lemere and Lasater[2] and by Moriarty and Mebane[3]

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[1] Medical Ethics, p 81 Cork, 1953

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[1] Levene, L. J , Lascelles C. F *Lancet*, 1959, ii, 675
[2] Lemere, F Lasater J H. *Amer J Psychiat* 1958 114, 655
[3] Moriarty J D, Mebane, J C. *ibid.* 1959 115, 941

The opposite view is expressed by Schorer and Lowinger [4] who recorded improvement in about one-fourth of psychiatric outpatients with depression treated for one month with deanol, and that improvement was greater in the psychotic than in the neurotic depressed patients

Chronic Schizophrenia

The criterion for inclusion was mood depression and/or hypochondriasis within a diagnosis of chronic schizophrenia under treatment in hospital

Atrol was given to 25 such patients, all males, as an adjunct to other treatments (occupational therapy, evening entertainments, weekend home leave in some cases, and phenothiazine derivatives) 11 patients were receiving chlopromazine, 7 perphenazine, 5 trifluoperazine, and 2 were on no tranquilliser

Atrol was not given with the purpose of counteracting phenothiazine-induced drowsiness, a symptom which responds satisfactorily to the known anti-parkinsonian drugs such as trihexyphenidyl 8 of the 23 patients having a phenothiazine derivative were in fact already having trihexyphenidyl as well

The duration of treatment varied from six to thirty-four days The maximum dosage ranged from 20 to 200 mg in one day, given as a single after-breakfast dose

3 patients had mild subjective relief of depression, 3 others became worse, expressing pre-existing bizarre ideas more floridly, and the remaining 19 patients were unchanged No unwanted clinical side-effects were seen

My impression is that atrol, in a varying dosage up to a maximum of 200 mg in one day, has not been of significant help to these chronic schizophrenic patients showing depression and/or hypochondriasis Other published results [5–7] have mostly been admitted to be inconclusive

I am grateful to Dr G Fitzpatrick and Dr C F Lascelles for their encouragement and permission to conduct this investigation, which was carried out at Cherry Knowle Hospital, Ryhope, Sunderland, to Dr H Merskey for his interest and advice throughout, and to Mrs G Swinhoe for clerical assistance

I also wish to record my thanks to Dr W I Simpson, of the research laboratories of Duncan, Flockhart & Co, for supplying the 'Atrol' This product has now been withdrawn by the manufacturers A different compound of the same deanol base is still being marketed by another firm

Booth Hall Children's Hospital,
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LESLIE J LEVENE

THE CIRCULATING CANCER CELL

SIR,—In your leading article of Aug 27 you say that "it is difficult to be sure that all the cells in the bloodstream which appear to be malignant are in fact so" This difficulty of identification is not a mere inconvenience leading to slight differences in the statistics from different centres It is a major factor which should make one hesitate before accepting the statistics at all

Searching for malignant cells is tedious and there is a tendency, especially if the diagnosis is known, to mark up dubious cells as "positive" A variety of large or immature cells can be found in white-cell concentrates from persons who have not got cancer, and these may occur in large numbers in patients who have We have, for example, found various forms of megakaryocytes or their bare nuclei in nearly every specimen of 60 examined from both normal people and patients with benign disease Cells which we believed to be *malignant* were found in only 7 out of 100 cases of malignant disease, and these 7 were all advanced cases with metastases [8] Without doubt, cancer cells do get into the circulation in clinically operable cases, but probably not continuously enough to be demonstrable in small random samples

If a worker claims to have found circulating cancer cells in operable cases without metastases, the onus should be on him to demonstrate the fact Only one of the workers mentioned in your article has given some case-histories with illustrations of the relevant cells and follow-up data from a few specific "curable" cases

The figures given in the literature should not be used to support a policy of giving cytotoxic drugs intravenously at the time of surgical operation, without a very thorough study of the morphological evidence from which the statistics have been compiled

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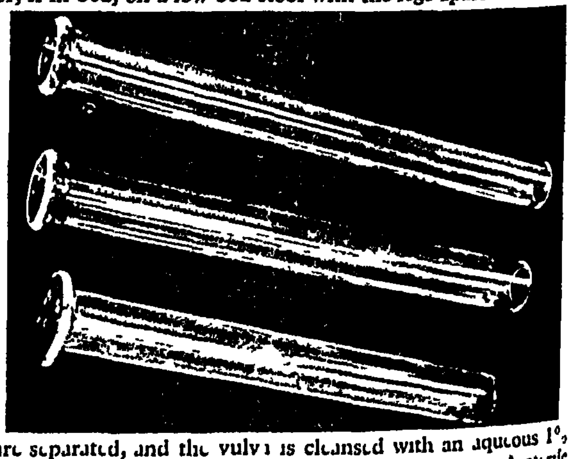
A I SPRIGGS
R F ALEXANDER

COLLECTING MIDSTREAM URINE SPECIMENS FROM FEMALE PATIENTS

SIR,—The risk of infecting the urinary tract by routine catheterisation is widely known [1] Catheterisation is, nevertheless, still commonly used to obtain a specimen of urine for laboratory examination and culture in female subjects The reason is that the techniques of obtaining an uncontaminated midstream specimen (e g, Hart and Magee [2]) are found by many nurses to be difficult, and because specimens so obtained often contain cellular debris from the vulva and yield contaminating organisms on culture

Our purpose is to describe a new and simpler way of collecting an uncontaminated midstream urine specimen from female subjects The method makes use of a glass tube approximately $^1/_2$ in in diameter and 6 in in length, one end of which is bell-shaped The tube is made in various sizes (see figure)

To collect a urine specimen the subject sits on a low stool, or, if in bed, on a low bed stool with the legs apart The labia are separated, and the vulva is cleansed with an aqueous 1% solution of cetrimide and dried with sterile gauze A sterile tube of appropriate size is chosen, the bell end placed in position over the urethral orifice, the tube held gently in position by the nurse, and the labia allowed to fall back over the tube The patient then voids urine and the *mid-portion* of the specimen is collected in a sterile jar



This method is simple and can easily be carried out by one operator, contamination of the specimen by contact with the labia is avoided, and it is possible to obtain specimens while menstruation is in progress

It must be emphasised that a high proportion of uncontaminated specimens can be obtained without the use of a tube if due care is taken Thus, in an experiment on 20 normal subjects carried out by one of us, 16 consecutive specimens were sterile without the use of the tube, and 20 out of 20 were sterile n the tube was used (The method of culture was to ulate 1 loopful of urine on a blood-agar and a McConkey- plate The possibility that the cetrimide solution used in nsing the vulva might have affected the bacteriology of the e was excluded by experiments in which urine so obtained shown to have no inhibitory effect on small numbers of *herichia coli* and *Staphylococcus aureus* subsequently added t [W A Gillespie, personal communication]) Because it mple to use, however, and because it ensures no contact ween urine and labia, it seemed probable that the routine of the tube in the collection of midstream urine specimens ld generally result in a higher proportion of uncon- unated specimens This, in fact, has been our experience, specimens have been collected from normal subjects by udent nurses and all were sterile on culture

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[4] Schorer, C E, Lowinger, P *Dis Nerv Syst* 1959, 20, 267
[5] Barsa, J A, Saunders, J C *Amer J Psychiat* 1959, 116, 255
[6] Pennington, V M *ibid* p 165
[7] Full, N *ibid* 1958, 115, 366
[8] Spriggs, A I *Proc R Soc Med* 1960, 53, 169

[1] *Lancet* 1960, i, 1231
[2] Hart, E L, Magee, M J *Amer J Nursing*, 1957, 57, 1323

he prototype of this collection tube was made by the department hysics, University of Bristol We wish to thank Mr L J Waller, the department of clinical pathology, Bristol Royal Infirmary, bacteriological assistance

H M LEATHER
M T HUTCHINGS

epartment of Medicine,
University of Bristol

EFFECT OF ELECTROSHOCK ON ERUM-LIPOPROTEIN-CHOLESTEROL LEVELS

SIR,—Alterations in serum-lipids associated with ctroshock therapy may be of considerable importance ice coronary occlusion is a well-recognised hazard of ch treatment[1-4], but as yet the effects of electroshock erapy on serum-lipids are not clearly established

van der Beek[5] observed small average increases in serum- olesterol in a majority of patients after electronarcosis, and nati et al[6] reported a slight lowering in serum-cholesterol els after shock treatment On the other hand, Kershbaum d coworkers[7] failed to demonstrate significant changes in rum-lipid concentrations in 14 subjects either as a result of ticipating electroconvulsion therapy or of the actual con- lsion

The effects of electroshock upon human serum-lipoprotein- olesterol levels has not been reported In order to study this rum-lipid fraction, blood was withdrawn from a group of 10 male psychiatric patients shortly before and immediately ter electroshock therapy Several of the women were sub- cted to repeated convulsive sessions Serum-lipoproteins ere separated electrophoretically on filter-paper and the nounts of cholesterol associated with the alpha and beta actions were measured by the method of Searcy et al[8] The first series of determinations performed on the sera from the 10 subjects indicated an apparent decrease in lipoprotein cholesterol following electroshock treatment However, differences in cholesterol values were so small that the significance was questionable Therefore, analyses for serum-lipoprotein-cholesterol were repeated on all serum samples in two separate laboratories using the same technique These data were in close agreement, and showed the same trend as the initial determinations The figures in the accompanying table are mean values of these replicate estimations

SERUM-LIPOPROTEIN-CHOLESTEROL LEVELS BEFORE AND AFTER SHOCK THERAPY

Subject	Age (yr)	Pre-shock cholesterol (mg per 100 ml)			Post-shock cholesterol (mg per 100 ml)		
		Alpha	Beta	Total	Alpha	Beta	Total
B C	33	74	221	295	61	177	238
		58	219	277	61	205	266
		63	181	244	61	174	235
		62	170	232	53	162	215
H R	58	75	274	349	69	246	315
		77	265	342	69	244	313
P M	33	91	191	282	76	180	256
		91	196	287	99	174	273
B H	41	90	232	322	71	219	290
H P	38	95	208	303	93	208	301
M M	31	57	132	189	55	129	184
M L	60	93	201	294	89	188	277
O D	44	95	242	337	109	208	317
H D	35	104	243	347	118	197	315
F B	72	72	199	271	73	200	273

It seems that following electroshock the distribution of cholesterol between alpha- and beta-lipoproteins was not much altered in the female patients studied In no instance was the amount of total lipoprotein cholesterol significantly elevated after this type of therapy On the other hand, a very slight but consistent depression in total cholesterol was observed in post-shock sera Mann and White[9] have also reported small but consistent decreases in serum-total-cholesterol of experimental animals subjected to various stresses These workers conclude that this reduction, apparently mediated through the adrenal gland, is a physiological response to stress

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Obituary

HAROLD DELF GILLIES

Kt, C B E, B A Cantab, F R C S, Hon F A C S

Sir Harold Gillies, who died in London on Sept 10 at the age of 78, was consulting plastic surgeon to St Bartholomew's Hospital, to the Ministries of Health and Pensions, and to the three Armed Forces His surgical lifetime spanned two wars and he himself treated many civilians and Service men and women, casualties of peace and war But not only his own patients owe a great deal to him Patients of plastic surgical units all over the country are in his debt, for he was the creator of his specialty in this country and the teacher of two generations of plastic surgeons

Universal Pictorial Press

He was born in Dunedin, New Zealand, in 1882, and he first achieved fame as an athlete He rowed for Cambridge in 1904 and also played golf for the university This skill he maintained, playing for England on a number of occasions up to 1926 He qualified from St Bartholomew's Hospital in 1908 and took the F R C S two years later His first interest was in ear, nose, and throat surgery

Early in the 1914–18 war he joined the R A M C and he found himself confronted with large numbers of patients with appalling facial mutilations He obtained permission to visit Paris to study with surgeons who were then among the leading European experts Of this beginning W K F writes

" Gillies' mind was soon made up He decided to start plastic surgery in the British Army He got in touch with the War Office and came home from France, and with the help of Arbuthnot Lane and his own drive and personality by 1916 he was established as a specialist in plastic surgery at the Cambridge Hospital, Aldershot At this time he knew little of his new subject, but his surgical experience, artistic temperament, endless patience, and boundless confidence carried him through He loved his patients and inspired confidence in them But he was still not satisfied He wanted a hospital of his own So he again approached Arbuthnot Lane and between them they persuaded the Red Cross to take over a large private house and grounds at Sidcup A hutted hospital was built and became known as the Queen Mary's Hospital, Sidcup There he was later joined by units from New Zealand, Canada, and Australia In fact Sidcup was the East Grinstead of the first war "

It was during this time that Gillies independently discovered the potentialities and varied applications of the skin tubed pedicle By 1920 he had established plastic surgery in Britain as a specialty and himself as its leading exponent After the war, though he still doubted whether there would be enough plastic work in peacetime to give him a living, he set up in private practice In due course he was appointed to the staff of Barts and of St James' Hospital, Balham It was at the latter hospital that he first met Mr Rainsford Mowlem Later they were joined by MacIndoe, and the famous " plastic " team was formed

Between the wars Gillies' international reputation grew and he was an honoured guest in many countries At home he played varied and important roles—as adviser to the Services and to the civilian authorities, and above all as a superb teacher and operator of the utmost distinction At the beginning of the late war, with Sir William Kelsey Fry, he was asked to organise plastic surgical units for the treatment of jaw injuries, and he himself supervised the large unit at Park Prewett Hospital, Basingstoke Soon after the war he helped to draw together the many surgeons of a younger generation who had recently entered plastic surgery, and to form the British Association of Plastic Surgeons He also took an important part in planning the plastic surgery services in the National Health Service He continued his work at Basingstoke until his 70th year, and until lately he was in private practice His book, the *Principles and Art of Plastic Surgery*, written and illustrated by himself with Dr Ralph Millard, which appeared in 1957, reflected his personality, for it was a classic exposition of the subject, yet both original and entertaining

Gillies was knighted in 1930 He was also a commander of the Order of the Dannebrog and the Order of St Olav He was an honorary fellow of the Royal Society of Medicine and of the American College of Surgeons

C R McL writes

" In 1953 Gillies' reception as the guest of the British Association of Plastic Surgeons was a memorable occasion worthy of his prodigious reputation as artist, golfer, motorist, oarsman, humorist—and surgeon Despite increasing years, his flair for brilliant improvisations and startling innovations, whether in theory or practice, continued There can be no doubt that this brilliant and versatile figure, with his questing mind and creative artistry, will always be regarded as the father of plastic surgery in this country "

By his first wife, Kathleen Margaret Jackson, Sir Harold Gillies had two sons and two daughters After her death in 1957 he married Marjorie Clayton, who survives him

MARJORY WINSOME WARREN

C B E, M R C S

It is hard to believe that only some fourteen years ago Marjory Warren could recommend the creation of geriatrics as a specialty[1] In fact she had already established herself as the earliest consultant in the proposed specialty She was one of the first to appreciate that, as she put it, " the medical profession, having succeeded in prolonging the life of men and women, must no longer fail in its responsibility to the elderly when they fall sick or become infirm " By her work at the West Middlesex Hospital she accepted that responsibility and offered many elderly people renewed activity and independence

She was educated at the North London Collegiate School, and after qualifying from the Royal Free Hospital in 1923 she held house-appointments at the Queen's Hospital for Children, Hackney, and clinical assistantships at the Royal Free Hospital and at the Elizabeth Garrett Anderson Hospital

In 1926 she became an assistant medical officer at the West Middlesex Hospital in Isleworth Nine years later, when the hospital took over the nearby poor-law infirmary, she was given the job of reorganising the care of several hundred chronic patients Though the patients were kept scrupulously clean and tidy she was appalled by the lack of classification which hindered adequate treatment " In the same ward were to be found senile dements, restless and noisy patients who required cot beds, incontinent patients, senile bed-ridden patients, elderly sick patients who were treatable, patients who were up and about all day, and unmarried mothers and infants " Her first act was to make a complete survey of all the patients, which showed that with adequate treatment many could leave hospital and return to their homes, and that even the incontinent and bedridden could be improved and given a fresh interest in life and some limited activity Her methods were especially successful in the management of cerebrovascular disease in the elderly

For many years she held the post of deputy medical director at the West Middlesex, and last year she was appointed C.B.E. She was a founder member of the British Geriatric Society and was international secretary of the International Association of Gerontology She spoke at many conferences abroad, and was on her way to give a paper at a meeting of the Medical Women's International Association at Baden-Baden when she met with a car accident She died in hospital in Metz on Sept 5 at the age of 62

A E B H recalls that Dr Warren was the newly elected president of the London Association of the Medical Women's Federation

" I suppose the last function Marjory Warren attended in her new capacity was when she came to a lunch given ten days ago at the South London Hospital for Women to 20 Japanese women doctors She had only just returned from a visit to California, where she had met a distinguished Japanese physician At once she seized on this chance encounter to make our Japanese friends feel they were on ground which, though foreign, was to some extent familiar, and to a great extent friendly Although only two of them spoke English, through those two she managed to carry her warm-hearted spontaneous capacity for setting people at their ease On the hospital authorities, who had never seen her before, she left an impression of a woman of outstanding personality She was indeed a remarkable and charming person who will be deeply missed by her friends, her colleagues, and above all the very great number of elderly patients (she would never er to them as old) who owe so much to her imagination and istructive handling of their many problems "

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[1] *Lancet*, 1916, i, 841

A L W writes

' Marjory Warren was a discoverer in the true, scientific ise, in that she looked at something all of us had taken for inted for years and saw it in a completely new light When arge group of the chronic sick was transferred to her care, e did not merely see a hopeless collection of human bodies, lpless, bedridden, apathetic, needing only devoted nursing d attendance to pressure points She saw rather a group of tients—human beings needing medical care and treatment, e stimulation of movement, friendliness, and activity that ves life With her intelligence and sound common sense she eated their disabilities, got them out of bed, mobilised their ffened joints and taught us that incontinence in the aged is ten more a matter of boredom and apathy than senility She owed that hemiplegics could be taught to walk again, however old, and that families would willingly care for their old lk if these were rendered reasonably mobile and self-helping t a time when acute hospitals were saying ' We can't do any ore for her—send her to the infirmary ', Marjory Warren as discovering for herself the principles of curative medicine r the elderly, and she may fairly be called the mother of eriatrics, though others have since added a scientific and ciological framework to the empirical basis she laid

"To work with her was an experience, and at least one clinical ssistant will not forget her brisk warm ward rounds with their areful insistence on accurate diagnosis, intensive nursing kills, and persistent unremitting exercise Most of all, there is he memory of the cheerful word for each patient, the knowedge of their particular problem, and the respect for the ignity and individuality of each Marjory was a delightful riend and *companion, full of humour* and warmth and itality, shot through and through with wisdom and good sense ne never turned to her in vain for help or advice Her tragic nd premature death gives one a sense of outrage that so aluable and happy a life has been cut short, but perhaps the est reaction, and the one she would have wanted, is to give hanks for such a life of integrity, service, and friendship "

ALICE CAMPBELL ROSE

M.B N Z, M R C P, D A

Dr Alice Rose, anæsthetist to the London Chest Hospital, died on July 25

She graduated in medicine in New Zealand in 1924, and after holding house-appointments in Dunedin she came to this country with a travelling scholarship She was drawn to work among children, and while holding a house-appointment at the Infants Hospital in Vincent Square she met Dr Kenneth Tallerman, whom she married in 1929 After her marriage she continued her work as a pædiatrician, and held appointments at several clinics, including the toddlers' clinic at Hammersmith Hospital, and was medical officer to a girls' school.

It seemed as though pædiatrics was to be her life's work, but at the beginning of the late war, in response to the need for anæsthetists, she turned to a new specialty She quickly established herself in it, taking the D A in 1942, and joining the staff of the London Chest Hospital in 1945 Of her work there a colleague writes

"To Alice Rose anæsthetics was not a routine occupation involving technical skill, it was an individual matter in which she made full use of her training as a physician. She was of the greatest help to many patients with social as well as medical problems, even though her official contact with them was the relatively remote one of an anæsthetist She was a remarkably handsome and young-looking woman, and to her inherent friendliness and sympathy was added a measure of dignity and poise which nothing could disturb

"In her home life she became Alice Tallerman, and she and her husband had many interests in common Many friends were made free of the contented yet stimulating atmosphere that surrounded them Their love of the countryside was given full play after the war when they settled in Essex, and those who visited them would never fail to be impressed by the serenity of their company "

Sir GORDON GORDON-TAYLOR

P W writes

" Gordon-Taylor was perhaps the best loved surgeon in the world, loved by his patients, his pupils, his colleagues, and by the rising generation of surgeons throughout the Commonwealth The men privileged to be appointed his registrar or house-surgeon had the best break of their lives By his devotion to his patients, by his skill and his charm, he so impressed them with the best in surgery that the lesson could never be forgotten And he did not lose interest when the period of apprenticeship was over but became a loyal friend, ever ready with help and encouragement Those of his pupils who later achieved success, and they are many, owe a debt to G-T that they can only acknowledge because it is too great ever to repay And the legion of younger surgeons from Australia, Ghana, India, New Zealand, Pakistan, and many other countries to whom he devoted the later years of his life must add their names to the finest memorial a man can have —My spirit lives in you "

A Danish surgeon writes

" To surgeons coming from other countries to study British surgery, Sir Gordon has been throughout his life a most appreciated adviser, always very helpful and friendly With his knowledge of surgery and surgeons, his sound judgment of the problems of each particular man, he was able immediately to put one ' on the right track ' In every case he took a great interest in securing that one did not waste one's time

" His scientific works on the surgery of the intestines, the parathyroids, carcinoma of the breast, and his hindquarter amputations were of the greatest interest and value to Scandinavian surgeons They are and will probably always be of lasting importance as milestones in pre-war surgery

" With his outstanding memory, his style in writing and speaking about his most extraordinary experiences by travelling to all the places where he was so well known and appreciated, he was able to entertain any surgeon of any age.

" All of us who have had the good fortune to meet and to listen to this ' Grand Old Man ' will remember him all our lives and will be grateful for all he gave in help, instruction, and friendship He was indeed a great surgeon and a good friend "

The British members of the International Society of Surgery, of which Sir Gordon was a vice-president, have received the following telegram from Prof Paul Martin of Brussels, the secretary-general of the society

" Deeply moved by the death of Sir Gordon Gordon-Taylor the officers of the Societe Internationale de Chirurgie send you their appreciation for the devotion manifested by our most distinguished membre d'honneur to the purposes of our Society Sir Gordon will live for ever in the hearts of our members "

Appointments

EDMUNDS, P N, M D, B.SC. Edin consultant bacteriologist, Fife district laboratory, Cameron Hospital, near Leven.

HUNTER, HENRY, M.B Lond senior assistant psychiatrist, to be designated deputy medical superintendent, Balderton Hospital, near Newark.

OWEN O E. M.B Edin, F R.C.S. consultant in general surgery, Bridgend General Hospital

ROBERTSON, J D, M.D Edin., F R.C.P E. F.F.A. R.C.S, D A. consultant anæsthetist, Royal Infirmary, Edinburgh

RYAN SHEILA RUTH M.B Lpool F.F.A. R C.S., D A., D OBST assistant M O, Middlesex County Council (Finchley and Hendon)

Notes and News

THE CONGO

In the Congo,[1] according to Dr J S McKenzie Pollock, W H O senior representative, the greatest medical need following the exodus of European medical personnel is attention to the preventive services, in order to preserve earlier gains—notably in the control of insect-borne disease Reports of many small, localised outbreaks of smallpox continue to come in. In some places, it seems, no vaccinations have been done in the past two years The limiting factors in organising a vaccination service are lack of supervisory staff and lack of security in some areas Some patients with leprosy are leaving institutions and returning to their villages because of the difficulty in maintaining food-supplies in the institutions Mosquito-breeding is reported to have increased substantially, and the numbers of cases of malaria and filariasis are increasing

W H O is placing its recruitment service at the disposal of the Congolese Government in order to obtain medical staff The aim is to staff the basic medical services on a scale of minimum requirement until Congolese doctors can gradually take over Plans for training Congolese undergraduate medical students are well advanced, and a programme is being established for Congolese medical assistants to take courses overseas to enable them to qualify as doctors

Medical teams from the following countries are in the Congo

Red Cross and Red Crescent teams —Czechoslavakia, Denmark, Finland, Japan, Holland, Poland, Canada (2), India, Pakistan, Australia (2), Greece, Norway, United Arab Republic, East Germany (3), Eire, Sweden, West Germany (2), Yugoslavia

Government teams —Ghana (3), Switzerland, Israel (3), U S S R (3)

REHABILITATION OF THE ARTHRITIC

At the final meeting of the world congress of the International Society for the Welfare of Cripples, held in New York from Aug 28 to Sept 2 with Prof Howard Rusk in the chair, it was announced that the society has been renamed the International Society for the Rehabilitation of the Disabled

As regards rheumatism the activities of the congress showed the urgent need for cooperation between medical specialists, lay experts, and the patients, if the arthritic person is to get an opportunity to help in his own rehabilitation and remain or become again a useful member of the community

Having previously formed world commissions on cerebral palsy, poliomyelitis, and paraplegia, the international society has for some years been considering the formation of a world commission on arthritis and rheumatism, through which information and experience could be exchanged At a meeting held with representatives of the International League against Rheumatism and the American Rheumatism Society, it was felt that there was no immediate need for a world commission but that an advisory committee on arthritis should be formed To organise this, a committee with Dr Francis Bach and Dr Ronald W Lamont-Havers as co-chairmen will meet representatives of the International League against Rheumatism and discuss means by which the two bodies can cooperate closely The social, vocational, and employment aspects of rheumatism are well represented in the society, which has affiliations in many countries, some of which are not yet represented in the league

Royal College of Obstetricians and Gynæcologists

Mr T F Corkill will deliver the William Meredith Fletcher Shaw lecture on Friday, Sept 23, at 5 P M, at the college, 27, Sussex Place, Regent's Park, London, N W 1 His subject will be New Zealand's Debt to British Obstetrics Tickets may be had from the secretary at the college

Medical Protection Society

The annual general meeting of this society will be held on Wednesday, Oct 5, at 3 P M, at 50, Hallam Street, London, W 1

Faculty of Radiologists

This Faculty will hold a meeting in Cardiff on Saturda Oct 15 At a joint meeting of the diagnosis and thera sections Prof Harold Scarborough will speak on medical wo in the Nigerian teaching hospital

Medical World General Practice Conference

This conference will be held on Sunday, Oct. 23, in t Victoria Halls, Bloomsbury Square, London, W C 1 Lo Taylor will give the opening address, and the subjects chos for discussion are the future of health centres, training f general practice, appointments systems in general practice, a problems common to the pharmaceutical industry and gene practitioners Further particulars and tickets (21*s*) may be h from the conference organiser, *Medical World*, 55, Russ Square, W C 1

Oliver Bird Trust

Dr Albert Tyler of the California Institute of Technolo will give the fourth Oliver Bird lecture on Monday, Sept. 2 at 5 P M, at the London School of Hygiene and Tropic Medicine, Keppel Street, W C 1 He will speak on immun logical approaches to fertility control

University College Hospital Medical School

Postgraduate demonstrations will be held at the medic school, University Street, Lóndon, W C 1, on Thursday a Friday, Oct 27 and 28 The annual dinner will be held at t Savoy Hotel, Strand, W C 2, on Oct 28, at 8 P M Tickets f the dinner (36*s*) may be had from the hon secretary, O Students' Association, at the hospital

Professional Nurses and Midwives Conference a London Nursing Exhibition

This conference and exhibition will be held, under t auspices of the *Nursing Mirror*, from Oct 10 to 14, at Seymo Hall, London, W 1 Details may be had from the organiser the exhibition, Dorset House, Stamford Street, S E 1

Association of Medical Records Officers

This Association is to hold a regional conference in Brighto on Sept 24 One of the speakers will be Dr M. A Heasma of the General Register Office, who will give a lecture o findings of the hospital inpatient inquiry Further particula may be had from Mr E S Beauchamp, Queen Mary Hospital, Sidcup, Kent

Royal Photographic Society of Great Britain

Medical Group —This group will hold an exhibition medical photography in the society's house, 16, Princes Ga London, S W 7, from Nov 7 to 22 The exhibition will b opened by Sir Robert Platt, P R C P, on Monday, the 7th at 7 P M

Sir Ifor Evans will give the inaugural address of the Royal Fr Hospital School of Medicine on Wednesday, Oct 5, at 3 P M., the Senate House, London, W C 1

On Wednesday, Sept 21, at 5 15 P M, at the Royal Free Hosp Gray's Inn Road, London, W C 1, Dr A G Bearn, of the Rockefel Institute, New York, will speak on genetics in medicine

A meeting of the Biochemical Society will be held in the depart ment of biochemistry, University of Glasgow, on Sept 29 and 3 The programme will include a colloquium on the biosynthesis o nucleic acids

At a meeting of the Anglo-American Medical Society to be he at the university department of chemistry, Lensfield Roa Cambridge, on Wednesday, Oct 5, at 8 P M, Dr Paul Wood w give a talk on recent advances in cardiology Further particula may be had from the hon secretary of the society, Mr A J Ed Cedar Cottage, March Road, Wimblington, Cambs

The Magsaysay award ($10,000) for public service at Manila h been given to Sir Henry Holland and his son, Dr Ronald Holla

The National Association for Mental Health have published t proceedings of their conference on *Mental Health at Home a Abroad*, held in London last March Copies (5*s* 6*d* post free) ma be had from the Association (Maurice Craig House, 39, Queen An Street, W 1)

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[1] See *Lancet*, Aug 13, 1960, p 358, *ibid* Sept 3, p 555, *ibid* Sept 10, p 607

The Lancet · Saturday 24 September 1960

INCIDENCE OF SURGICAL WOUND INFECTION IN ENGLAND AND WALES

A report of the Public Health Laboratory Service

THERE is a general impression that postoperative wound psis is becoming more common. This belief is probably ised on reports of outbreaks of exceptional severity, ith sepsis-rates between 10% and 37%, and effects on itients varying from negligible inconvenience to pro-isely discharging sinuses and death, or from a few extra iys to many months in hospital. These figures from itbreaks of infection are probably reliable because they ere collected at times when the units concerned were sepsis conscious " and all the manifestations of wound ifection were carefully noted. Attempts to determine :psis-rates in non-epidemic times have been less satis-ictory General inquiry of hospitals yields widely ivergent answers Some admit that they are uneasy bout sepsis, whilst others stoutly deny that it occurs at ll. Retrospective analysis of clinical records is almost seless because only sepsis of the grossest kind is recorded ı them. It thus appears that only an investigation lanned for the specific purpose can yield a true estimate f the general frequency and cost of wound sepsis

A few investigations of this type have already been nade in single hospitals In Britain, Clarke (1957) :eported a sepsis-rate of 13 6%, causing a mean extra tay in hospital of 8 1 days, Jeffrey and Sklaroff (1958) ound that sepsis developed in 26 1% of clean operation vounds, and that this was " serious " in 9 8%, Burnett :t al. (1958) recorded a sepsis-rate of 7 6% There are imilar reports from Australia, Canada, and the United States

These reports suggest that sepsis-rates throughout the country may be much higher than is generally realised. The present investigation was therefore planned to give information on the incidence of wound sepsis and its cost in terms of loss of life and length of stay in hospitals where there is no special complaint of sepsis This was the main object of the investigation, but the opportunity was taken to determine the relationship between wound sepsis and some of the circumstances that might determine its development. These were nasal carriage of *Staphylococcus aureus* by the patient before operation, age and sex, nature and duration of the operation, length of incision, and presence or absence of a drainage tube

Methods

General Plan of the Investigation

The hospitals studied were selected on the basis of convenience and not because of any special concern over the incidence of sepsis For the main survey all were hospitals for which one of the laboratories of the Public Health Laboratory Service carried out the routine bacteriology, and in each centre the investigation was supervised jointly by the bacteriologist and one or more of the surgeons.

There were three phases of the study

1 *A pilot survey* in four hospitals, lasting one month during the summer of 1957, which demonstrated the practicability of the general plan and revealed the need for some small but important changes of procedure

2. *The main survey* from August, 1957, to April, 1959 Eleven hospitals took part, though not all for the whole period, but nine kept records for at least twelve months

3 *A short survey*.—During one week in the last month of the trial, the results of the main participants were supplemented by those from nine other hospitals This was intended as a check on the results of the main survey and to give the whole investigation a wider geographical representation.

Selection of Patients

In each unit, the patients included in the survey were all whose operation involved an incision through healthy skin, except those operated on because of sepsis—such as incision of an abscess or drainage of an empyema. Operations on the lower urinary tract, rectum, or anus and on accidental wounds were excluded, not because sepsis in them was thought to be any less important but because infection added in hospital is easier to recognise in previously clean wounds, which were therefore used as the most convenient indicators of hospital infection. Patients with appendix abscess and those with other abdominal disease who were found to have peritonitis at the time of operation, mostly due to perforated duodenal ulcers, were included but are presented separately in several of the tables

Records

Records were kept for each patient on a special form.

On the day of admission to hospital a nose swab was taken from each patient and was cultured for *Staph. aureus* and *Streptococcus pyogenes* by direct and enrichment methods If more than a week elapsed before the operation, the nose was swabbed again on the day of operation. All strains isolated were stored and most strains of *Staph. aureus* were submitted for phage typing

Immediately after the operation the surgeon recorded details of it and his estimate of the time the patient would be in hospital.

During the postoperative period the wound was examined at the time of the first dressing, then weekly, or more often if abnormalities were noticed, and then again on the day of discharge from hospital. For a great many operations the wound was in fact examined only once because the postoperative dressing was not removed until the wound was healed and the patient ready for discharge. The state of the wound was recorded at each examination by the surgeon, bacteriologist, ward sister, registrar, or resident doctor, but efforts were made to ensure that at least half of the wounds, and all those not healing normally, were seen by the surgeon or bacteriologist.

Swabs were taken from nearly all wounds at the time of the first dressing and at any later examination if they were not healing cleanly All organisms isolated were noted in the postoperative record Strains of *Staph. aureus* from wounds were typed.

After the patient's discharge from hospital, the surgeon and bacteriologist jointly decided whether there was clinical and bacteriological evidence of infection.

Results

From the pilot and main surveys in twelve hospitals we had records for 3002 operations, and from the short survey in some of these and in the ten other hospitals we had a further 274 Since the results from the three surveys were very similar, most of the analyses presented here are based on the total of 3276 operations Clinical records were available for them all, though they were

TABLE I—INCIDENCE OF SEPSIS AND INFECTION WITH PATHOGENIC BACTERIA (ALL WOUNDS WITH BACTERIOLOGICAL RESU AVAILABLE EXCEPT THOSE IN PATIENTS WITH PERITONITIS)

Clinical state of wound	Wounds		Pathogenic bacteria isolated from wound during convalescence					No i which pathoge isolate
	No	% of total	*Staph aureus* Alone	*Staph aureus* With other pathogens (mainly coliforms)	Coliform organisms alone	Other pathogenic bacteria	Total	
Healthy	2366	86	188	14	106	47	355	2011
Septic	380	14	172	57	65	14	308	72
Discharging pus	182	6 6	96	37	31	7	171	11
Serous discharge, gaping, healing by granulation, or general erythema, never purulent	139	5 1	54	18	26	4	102	37
Stitch abscess only	19	0 7	10	1	3	2	16	3
Marginal erythema only	40	1 5	12	1	5	1	19	21
All wounds	2746	100	360	71	171	61	663	2083

not invariably complete in every detail, 403 of the 2840 clinically healthy and 13 of the 436 clinically septic wounds were not examined bacteriologically There were 58 patients who had an appendix abscess and 56 others who were found to have peritonitis at operation, these have been excluded from tables I and IV

We have used the term " septic " to refer to clinically manifest disease in the wound, and " infected " to mean the presence of pathogenic bacteria, including as pathogens coagulase-positive staphylococci, hæmolytic streptococci, fæcal streptococci, and coliform bacilli Included in the coliform group were *Escherichia coli*, *Klebsiella* species, *Proteus* species, and paracolon bacilli

General Incidence of Sepsis and Infection

Of the 2746 wounds (excluding those in patients with peritonitis) for which we had complete clinical and bacteriological information, 380 (14%) showed some signs of sepsis during healing and 663 (24%) yielded pathogenic bacteria on culture (table I), 308 (11% of the total) were septic and yielded pathogenic bacteria Because it was very largely the healthy wounds for which bacteriological records were not available this last rate, when calculated on the whole population (i e, including those not examined bacteriologically), was slightly lower (9 7%)

Almost half the wounds reported as septic discharged pus at some time and only 59 (16%) had no more than a stitch abscess or marginal erythema Pathogenic bacteria were found in 308 (81%) of the 380 septic wounds and in 171 (94%) of the 182 purulent wounds *Staph aureus* was found in 229 (60%) of the septic wounds in 202 (9%) of the healthy wounds

After *Staph aureus*, the commonest pathogens septic wounds were coliform organisms, which occur together with staphylococci in 50 (13%) and alone 65 (17%)

Nine hospitals contributed records of 100 or m wounds to the main survey (table II), but two of th (A and B), in one city, contributed nearly half the to

TABLE II—SEPSIS-RATES BY HOSPITALS

Hospital	Total no of patients (1)	% of total clinically septic (2)	% septic and infected with pathogens (3)	% examined and healthy but infected with pathogens (4)
A	816	13 0	11 4	17 0
B	736	13 9	12 9	16 7
C	316	8 9	4 7	14 9
D	308	13 3	9 7	6 9
E•	166	1 8	1 2	3 8
F	165	9 7	7 9	33 9
G†	164	12 8	9 1	9 9
H	110	26 4	21 8	29 6
I	102	21 6	12 7	6 3
J	55	23 6	16 4	16 7
K	51	9 8	7 8	6 5
L‡	13	7 7	7 7	25 0
Totals				
main survey	3002	12 9	10 5	15 0
short survey	274	17 9	11 3	15 4
Aggregate	3276	13 3	10 6	15 1

Hospitals A and B are in the same city
• Orthopædic operations only
† Thoracic operations only
‡ Took part in pilot survey only

TABLE III—INCIDENCE OF SEPSIS AND INFECTION AFTER VARIO OPERATIONS (ALL PATIENTS)

Operation	All patients			Patients with healthy wounds		Pat wi infec wou % w sep (6
	No (1)	% with sepsis and infection (2)	% with staphylococcal sepsis (3)	No examined bacteriologically (4)	% infected with pathogens (5)	
Gallbladder	247	20 6	14 9	172	17 4	63
Breast	188	15 4	12 7	122	6 6	78
Miscellaneous abdominal	373	12 9	11 0	275	18 5	49
Varicose veins	179	11 7	8 9	98	24 5	46
Thorax	171	8 8	7 5	148	10 1	50
Gastrectomy	240	8 7	5 8	189	17 6	38
Sympathectomy	39	7 7	7 7	31	12 9	42
Hernia	437	7 3	5 9	348	21 3	30
Appendix	550	6 7	2 3	415	9 4	48
Thyroid	165	4 2	3 6	140	12 9	28
Miscellaneous orthopædic	208	2 9	2 9	165	4 9	42
Meniscectomy	64	0	0	62	8 1	0
Miscellaneous	301	12 0	10 6	200	23 0	43
Appendix abscess	58	43 1	22 4	31	22 6	78
Other abdominal with peritonitis	56	21 4	10 7	40	12 5	70

The incidence of septic infected wounds varied betwe 21 8% and 1 2% The latter figure was from an orth pædic service, the lowest figure in a general hospital w 4 7% There were some curious differences in t proportions of infected but healthy wounds (column which we have not been able to explain, they were n due to obvious differences in technique

No consistent seasonal differences could be detected

Incidence of Sepsis and Infection after Different Operatio

Table III shows the proportions of the wounds th were both infected and septic (column 2) or infected bu clinically healthy (column 5) for the various categories operation Only three categories had sepsis-rates belo 5%, and four (other than those with peritonitis) had rat over 10% The highest rates were, not unexpectedly, the two groups of patients with peritonitis present operation, for which " sepsis " refers to disease in th parietal wound, but clean gallbladder operations had

BLE IV—INCIDENCE OF SEPSIS AND INFECTION IN RELATION TO ARIOUS FACTORS (ALL PATIENTS EXCEPT THOSE WITH PERITONITIS)

—	All patients		Patients with healthy wounds		Patients with infected wounds
	No	% with sepsis and infection	No examined bacteriologically	% infected	% septic
ex					
Male	1619	10·3	1232	17·4	43·7
Female	1540	9·3	1132	12·4	50·5
ge (yr)					
0–29	766	6·4	566	11·8	42·2
30–59	1647	7·9	1256	14·7	41·3
60+	702	18·1	477	21·2	55·7
ength of incision (in)					
0–6	2189	6·9	1672	14·9	37·6
More than 6	887	16·3	632	15·2	60·2
uration of operation (min)					
0–30	1102	4·3	848	9·9	35·9
31–60	1086	9·8	813	16·1	44·7
61+	729	17·7	511	20·7	54·9
rainage					
Not inserted	2260	6·7	1727	14·2	51·0
Inserted	885	16·5	633	17·2	57·2
otal	3162	9·7	2366	15·0	46·4

Totals for the separate classifications do not agree because individual items f information were missing from some records

ate nearly as high In all categories but one, symptomless nfection had an incidence rather higher than clinical epsis, but in the four categories with the high sepsis-rates epsis developed in most of the wounds that became nfected

Various Factors Correlated with Sepsis

The differences in sepsis-rates between the operations must to some extent reflect differences in the types of patient who needed the various operations, and also the nature of the operation itself Five such factors are analysed in table IV, which refers to all patients other than those with pre-existing peritonitis Increasing age, length of incision, and duration of operation were all associated with an increase in sepsis-rate Sepsis developed more often in drained wounds than in undrained The incidence of asymptomatic infection showed the same trends but to a lesser degree

The different factors analysed in table IV are clearly interrelated, old people tended to have operations of longer duration than young, long incisions were more often drained than short, and so on More complex statistical analysis by Dr O M Lidwell (to be published elsewhere) suggested that each of four factors—age, length of incision, duration, and drainage—had an independent effect in leading to an increased sepsis-rate

Type of Infection in Various Operation Wounds

Although *Staph aureus* was the predominant pathogen it was not equally common in the septic wounds of different types of operation (table V) Coliform infections were particularly common after operations in the abdominal cavity, but they were by no means confined to these operation wounds The proportion having pure coliform infections was also higher in the clinically healthy than in the septic wounds

Relation of Staphylococcal Infection to Nasal Carriage

Nasal swabs showed 821 (27%) patients to be carriers of *Staph aureus*, 8·9% of the carriers showed staphylococcal sepsis of their wounds during convalescence, compared with 7·1% of the non-carriers (table VI) This difference is not statistically significant (S E diff = 1·06)

Of the 601 patients who had staphylococci of a defined type in their nose (i e, excluding the 94 with untypable strains and the 126 whose strains were not sent for typing), 63 (10·5%) developed staphylococcal sepsis, in 24 (4·0%) the staphylococcus from the wound was the same type as that in the nose and in 36 (6·0%) it was different, in the remaining 3 the phage-type comparison was inconclusive

TABLE VI—RELATION OF STAPHYLOCOCCAL SEPSIS TO NASAL CARRIAGE

—	Patients with			
	Staph aureus in nose (821 patients)		No *Staph aureus* in nose (2235 patients)	
	Sepsis at 1st dressing	Sepsis later	Sepsis at 1st dressing	Sepsis later
No with staphylococcal sepsis	51	22	103	55
No with wound staphylococcus				
Same as nose strain	22 (*43%*)	2 (*9%*)	—	—
Doubtfully same nose strain	3 (*6%*)	0	—	—
Different from nose strain	23 (*45%*)	13 (*59%*)	—	—
Not typed	3 (*6%*)	7 (*32%*)	—	—
Total sepsis	73 (*8·9%*)		158 (*7·1%*)	

Nasal carriers of a few phage types of staphylococci appeared to have an above-average risk of self-infection Thus, of the 74 who carried strains of types 80, 52/52A/80, or 52/80 in the nose before operation, postoperative sepsis developed in 11 (14·9%), in 10 cases with a staphylococcus of the type found in the nose

Staphylococci of phage-group II, and of the miscellaneous groups were rare in the septic wounds (table VII), it was not therefore surprising that no nasal carriers

TABLE V—BACTERIA RESPONSIBLE FOR SEPSIS AND INFECTION IN VARIOUS OPERATION WOUNDS (ALL WOUNDS WITH PATHOGENIC BACTERIA)

Operation	Septic wounds					Healthy wounds				
	No	% with				No	% with			
		Staph. aureus total	*Staph aureus* alone	Coliforms alone	Other pathogens		*Staph aureus* total	*Staph aureus* alone	Coliforms alone	Other pathogens
Miscellaneous orthopædic	6	(100·0)	(66·7)	0	0	8	(75·0)	(75·0)	(25·0)	0
Sympathectomy	3	(100·0)	(100·0)	0	0	4	(100·0)	(75·0)	0	0
Thorax	15	86·7	66·7	13·3	0	15	80·0	66·7	13·3	6·7
Thyroid	7	(85·7)	(85·7)	(15·3)	0	18	77·7	72·2	22·2	0
Miscellaneous abdominal	48	85·4	54·2	10·4	4·2	51	56·9	56·9	33·3	9·8
Breast	29	82·7	72·4	13·8	3·4	8	(75·0)	(62·5)	(25·0)	0
Hernia	32	80·2	68·7	15·6	3·1	74	58·0	54·0	29·7	25·7
Varicose veins	21	76·2	42·9	23·8	0	24	41·6	33·3	58·3	0
Gallbladder	51	72·5	58·8	23·5	3·9	30	66·6	63·3	20·0	13·3
Gastrectomy	21	66·6	47·6	19·0	14·3	33	69·7	66·7	15·1	15·1
Appendix	37	35·1	16·2	56·8	8·1	39	33·3	33·3	46·1	20·5
Appendix abscess	25	52·0	24·0	44·0	4·0	7	(14·3)	(14·3)	(85·7)	0
Miscellaneous abdominal with peritonitis	12	50·0	16·7	16·7	33·3	5	(40·0)	0	(40·0)	(20·0)
Miscellaneous	38	88·2	65·8	15·8	5·3	46	65·2	60·9	26·1	8·7

Percentages based on less than 10 patients are in parentheses.

TABLE VII—PERCENTAGE PHAGE-TYPE DISTRIBUTION OF STAPHYLOCOCCI FROM WOUNDS

Phage group and type	Hospitals other than A and B		Hospitals A and B		No of hospitals with type represented
	Septic	Healthy	Septic	Healthy	
I					
80	25 9	13 7	10 1	11 0	10
52/52A/80, 52/80*	6 2	5 3	47 3	13 8	6
29	1 2	10 5	1 4	1 1	8
29/52/80 &c	6 2	3 2	0 7	1 1	6
Others	7 4	3 2	6 1	5 5	
Total	46 9	35 0	65 6	61 7	
II, total	1 2	8 4	4 7	5 5	
III					
75/77	6 2	4 2	0 7	2 7	6
47/53/75/77 &c †	6 2	2 1	0	1 1	3
6/47/53/75	0	5 3	0 7	0	1
6/7/42E/47/53/54 &c	1 2	3 2	2 0	1 4	4
7/42E/47/53/54	1 2	2 1	1 4	1 4	3
77	2 5	0	2 0	0	4
53	2 5	0	2 0	0	3
75	3 7	0	0	0	2
Others	6 2	1 1	7 4	6 9	
Total	29 7	17 9	16 2	13 7	
Mixed, total	4 9	2 1	6 1	1 4	
Miscellaneous, 187	0	2 1	0	0	2
Untypable	17 3	33 7	7 4	17 8	
No of wounds with staphylococci typed	81 100 0	95 100 0	148 100 0	73 100 0	

* Including a small number of strains reported as 80+

† Including strains with the patterns 53/75/77, 47/75/77

of such staphylococci showed sepsis apparently due to self-infection For some unexplained reason, the 106 nasal carriers of group-II strains also had a very low (0 9%) cross-infection rate

There is a suggestion, though the figures are small, that sepsis present at the time of first dressing was more commonly due to a staphylococcus found in the nose than was sepsis developing later (table VI) In a third of the cases of symptomless wound infection in nasal carriers, staphylococci from the wounds were of the same phage type as the nasal strain

Interval between Admission to Hospital and Operation

The sepsis-rate was higher for patients who were in hospital eight days or more before having their operation than for those who had the operation soon after admission (table VIII) We found no explanation for this but cannot exclude the possibility that delay in performing the operation is often associated with other factors that favour sepsis such as greater age of the patient and longer and more severe operations.

Phage Type of Staphylococci

The phage types of staphylococci from the septic and healthy wounds are shown in table VII Since a large proportion were derived from the wounds in two hospitals in one city, these have been presented separately Phage-type 80 was by far the commonest type in the hospitals other than A and B, where strains with the related patterns 52/52A/80 and 52/80 were even more common It was curious to observe that no type-80 strains were found in the wounds examined in five of the hospitals in the North of England, the type was found in all but one of t eleven contributing hospitals in the South and Sou West and Wales Staphylococci of type 29 were mu commoner in healthy than in septic wounds, as we untypable strains

TABLE VIII—INTERVAL BETWEEN ADMISSION TO HOSPITAL AND OPERATION, IN RELATION TO SEPSIS

Days in hospital before operation	No of patients	% in whom staphylococcal sepsis developed
0–2	2103	6 6
3–7	762	7 9
8+	388	11 9

Length of Stay in Hospital

At the end of each operation the surgeon was asked predict the patient's length of stay in hospital We ha tried to measure the consequences of sepsis by determini the difference between the expected stay and the actu stay For this analysis we have excluded all patie who died, who were kept in hospital for any reas (medical or non-medical) not associated with wou healing, or who were transferred to a convalescent hor before the wound was healed

The results for the 2688 patients suitable for analy are given in table IX For those with healthy a uninfected wounds the surgeons' estimates were ve accurate, the average stay in hospital being less than o day shorter than predicted There was a suggestion th the apparently healthy but infected wounds may ha suffered a slight delay in healing There was also sor delay with the septic wounds from which no pathoge were isolated, it will be remembered that most of the showed only rather trivial signs of sepsis (table I) T patients whose wounds were septic and infected wi pathogens had a mean excess stay of 7 3 days, b within this group the discharging wounds had excess of over 10 days, whereas stitch abscesses a marginal erythema were associated with less than 2 day excess

The predicted stay for the whole group of 2688 patien was 32,442 days, but, allowing for the fact that in uncomplicated cases the patients left hospital earlier tha predicted, the total "uncomplicated" stay woul actually have been 30,383 days if sepsis or infection ha developed in no case The excess of 1772 days due t the septic patients was thus 5 8% of the probabl uncomplicated stay

TABLE IX—LENGTH OF STAY IN HOSPITAL

State of wound		No of patients with records available	Mean no of days in hospital		No of days excess or deficit, for group
Clinical	Bacteriological		Expected	Actual less expected	
Healthy	Not infected	1736	11 8	−0 766	−1330
"	Not known	347	10 3	−1 058	− 367
"	Infected	306	13 2	−0 203	− 62
Septic	Not infected	58	13 8	+1 155	+ 67
"	Not known	8	9 0	+0 125	+ 1
"	Infected	233	14 9	+7 313	+1701
Discharging pus		126	15 8	+10 389	+130
Granulation, exudate, &c		80	13 5	+ 1 512	+ 36
Stitch abscess only		11	15 3	+ 1 929	+ 2
Marginal erythema only		13	15 1	+ 0 538	+

The mean excess stays in days for the septic patients in various operation groups were as follows appendix abscess 12 4, breast 9 2, appendix 8 1, gallbladder 6 1, hernia 5 8, gastrectomy 4 3, varicose veins 4 3 These are to be compared with the mean excess for all septic patients of 7 2 days For the same set of patients pure staphylococcal sepsis was associated with an excess of 5 3 days, pure coliform sepsis with an excess of 6 5 days, and mixed staphylococcal and other pathogens (mostly coliforms) with an excess of 14 0 days

aths

Altogether 58 (1 8%) of the patients in the survey died, of those who died were 70 or more years old and 12 ore were aged 60–70 The death-rate was higher in the tients in whom wound sepsis developed (4 1%) than those in whom it did not (1 5%), but this was perhaps be expected since sepsis developed more commonly the old people Our records of the cause of death ere not sufficiently detailed, but it seemed that only 1 the deaths could be attributed without question to ound sepsis Besides this, there were a few in which e evidence was suggestive but not conclusive

Discussion

The aim of this investigation was to obtain a broadly ised estimate of the amount of postoperative wound psis now occurring in hospitals in England and Wales hough 1652 of the 3276 patients in the survey were in vo hospitals in one city, the fact that their sepsis-rate as very close to that of the remaining 1624 patients in neteen other hospitals justifies one regarding the cidence of sepsis—9 7% of all wounds—as a useful stimate of the figure for general hospitals Almost half e patients with "septic" wounds had discharge of ank pus so that, even on this more restricted criterion, e incidence of sepsis would have been about 5%. epsis was not confined to the more complex operations, nd even herniorraphies had a sepsis-rate of over 7% hese rates are much higher than many clinicians would egard as acceptable, and they seem to confirm the npression given by the local surveys, mentioned earlier, hat surgical sepsis is commoner than most people have hought. Yet they probably underestimate the full roblem because certain types of infection, such as those fter surgery of the lower urinary tract, were excluded rom the survey but are known to be very common

Higher sepsis-rates are associated with older patients, arger incisions, longer operations, and the use of drainage ubes Detailed statistical analysis to show that each of hese has an independent effect will be presented elsewhere They are not factors that can be controlled in an ttempt to prevent sepsis, but it is important to know of heir association with it so that allowance may be made or them when sepsis-rates from different surveys are being compared The higher rates, of sepsis in nasal carriers of some strains of staphylococci and in patients admitted to hospital a week or more before operation appear to deserve further study

Measurement of the "cost" of sepsis is much more difficult If our figures are applicable to the 1 5 million surgical operations performed annually in all hospitals in England and Wales, the total excess stay in hospital due to sepsis may be about 1,000,000 days per year, or about 3% of the total bed-occupancy of acute hospitals The monetary cost of this may be about £3 3 million, or about 0 5% of the total cost of the National Health Service, and to this must be added the cost of sickness insurance, loss of wages, and so forth But the obvious conclusion—that some £5 million might be saved by the elimination of sepsis—is not necessarily true, and indeed it may be necessary to spend more than £5 million each year if we are to make any substantial progress towards eliminating sepsis It may be better to regard as a challenge to our medical skills the thought of 75,000 people who had clean operation wounds that discharged pus, of the 5000 whose stay in hospital was prolonged by a month or more, and of the, perhaps, 500 who died from sepsis

Summary

A survey was carried out to determine the incidence of sepsis after surgical operations and its cost in terms of excess stay in hospital A total of 3276 surgical operations in twenty-one different hospitals were studied clinically, and (in 2860 cases) bacteriologically during convalescence

9 7% of the wounds were affected by some postoperative sepsis and yielded pathogenic bacteria on culture The sepsis-rate in different hospitals undertaking general surgery varied between 4 7% and 21 8% The highest sepsis-rates after clean operations were for cholecystectomy (21%) and breast operations (15%), and the lowest were for orthopædic operations (2%)

Greater age of the patient, length of preoperative stay in hospital, length of incision, and duration of operation were all associated with increased sepsis-rates, as was the use of a drainage tube *Staphylococcus aureus* was the commonest pathogen, but infection with coliform organisms was also common

Nasal carriers of *Staph aureus* had only a slightly higher postoperative-sepsis rate than non-carriers (8 9% compared with 7 1%), but nasal carriers of a few phage types of staphylococci had a considerably higher sepsis-rate

Patients whose wounds healed without sepsis or infection left hospital, on average, 0 8 days earlier than had been predicted on the day of operation, those with sepsis and infection had an excess stay of 7 3 days over that predicted

58 of the patients in the survey died, but in only 1 case was death definitely attributable to wound sepsis

We are grateful to the clinicians who allowed this survey to be made in their wards and who, together with their nursing staff, kept many of the records that were needed for it The following took part in the investigations in the hospitals

Surgeons and physicians —Mr D S M Barlow, Mr J P Childs, Dr W Clancy, Mr L G Cruickshank, Mr J E H Ellis, Mr H De, Mr W J Fraser, Mr E W Grahame, Mr S G Griffin, Mr F M Hanna, Mr D H C Harland, Mr A H Haxton, Mr R. M Hill, Mr P W Houghton, Mr R E Isaac, Mr B Isserlin, Mr M Leitch, Mr D H Lloyd, Mr S N Lytle, Mr K C McKeown, Mr G H Marshall, Mr F Masina, Mr H Dendy Moore, Mr C P Nicholas, Mr F J P O'Gorman, Mr S Pappworth, Mr G Parker, Dr W C Pinkney, Mr L W Plewes, Mr T Rountree, Mr G H A Simmons, Miss B V Slesser, Mr D J Ross Steen, Mr T Russell Stevens, Mr B R Sworn, Mr B Thomas, Mr L B Williams, Mr D C Williams

Bacteriologists —Dr R Blowers,* Dr D R Christie,* Dr P B Crone, Dr D G Davies, Dr E H Gillespie,* Dr R J Henderson,* Dr H D Holt, Dr K E A Hughes,* Dr R I Hutchinson, Dr C H Jellard,* Dr E M. Mackay-Scollay,* Dr N S Mair,* Dr B Moore,* Dr H D S Morgan,* Dr D J H. Payne, Dr. Lewis Parker, Dr R. Pilsworth, Dr H G Smith, Dr J W G Smith, Dr Marjorie V Sudds, Dr G H Tee, Prof Scott Thomson,* Dr Margaret Wilson

* The bacteriologists indicated with an asterisk, together with Dr R. E O Williams and Dr J C. McDonald, constituted the working party that organised the investigation

The results were analysed and the report was prepared by Dr R. E O Williams, Dr J C McDonald, and Dr R. Blowers

We are indebted to the Registrar General of England and Wales for estimates of the number of surgical operations performed each year

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HYDRONEPHROSIS

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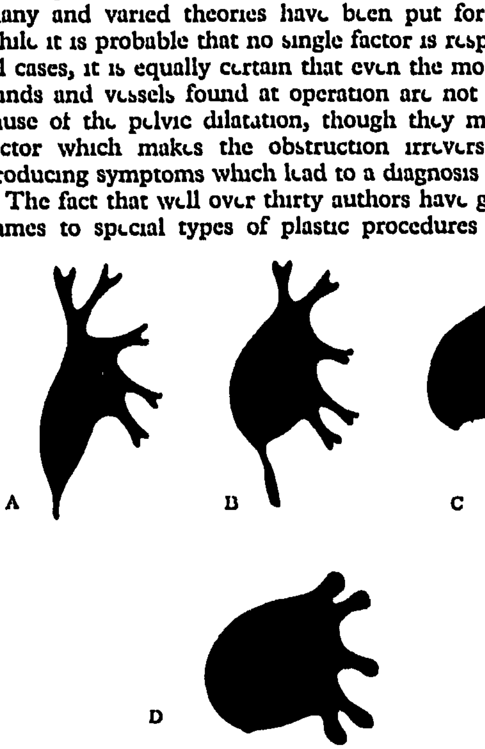
RENAL surgery is becoming increasingly conservative, and most urologists today consider that a nephrectomy, though all too often necessary, is nevertheless an admission of failure This view has been greatly sustained by such factors as earlier and more accurate diagnosis, improving anæsthesia, and the more effective control of urinary infection. This conservative trend is particularly well demonstrated in the approach to hydronephrosis due to disease at the pelvi-ureteric junction Not many years ago "nephrectomy for pyonephrosis" was relatively common on any major operating-list, while a "conservative operation for hydronephrosis" was distinctly rare

In contrast, the St Peter's and St Paul's Hospital report for 1958 records only 6 cases of pyonephrosis (4 nephrectomies) but there were 54 cases of hydronephrosis, only 12 of which were submitted to nephrectomy Therefore, not only are hydronephrotic kidneys being detected earlier before they have become frank pyonephroses, but even the infected hydronephroses may now be amenable to conservative surgery, so that the only indication for nephrectomy in such cases is the almost complete absence of any useful renal parenchyma

The ætiology of hydronephrosis has aroused controversy since the condition was first recognised, and many and varied theories have been put forward, but while it is probable that no single factor is responsible in all cases, it is equally certain that even the most obvious bands and vessels found at operation are not the initial cause of the pelvic dilatation, though they may be the factor which makes the obstruction irreversible, thus producing symptoms which lead to a diagnosis

The fact that well over thirty authors have given their names to special types of plastic procedures (many of which are merely modifications or combinations of predecessors) indicates that the ideal operation has not yet been discovered, but a study of the ætiology makes it obvious that no one operation will ever suffice to effect a cure when there are a variety of causes It seems that future progress in preserving hydronephrotic kidneys depends more upon a careful study of the causes than upon the devising of new surgical techniques, and it is relevant to consider the various new physiological conceptions concerning the conduction of urine from the renal tubules to the bladder



A, B, and C are variations of the normal pelvis and pelvi-ureteric junction (A) The most common type of funnel pelvis The pelvi-ureteric junction is ill defined and seems to be open at all times This pelvis is practically empty in the upright position (C) The opposite extreme; a rounded pelvis with a tonic junction found in less than 10% of normal individuals This pelvis retains a small quantity of urine even in the upright position due to the tonicity of the junction which remains closed rather than wide open The difference between the extreme range of the normal C, and a true hydronephrosis D, is only a matter of degree

Emptying Mechanism of the Renal Pelvis

The theory that there is a set rhythm of conduction from calyces to pelvis to ureter to bladder is not borne out by hydrostatic or electrical experimentation (Trattner 1935, Lapides 1948, Hanley 1953), while actual visual observations using the X-ray image intensifier show that the pattern of conduction varies considerably, not only from one individual to another, but from minute to minute in the same kidney (Hanley 1955) Each particular segment of the system, be it calyx, pelvis, or ureter, reacts to the presence of fluid in a characteristic manner, the only stimulus to contraction being the presence of fluid in the lumen so that the movement pattern will obviously vary with the volume of urine excreted

The pressure gradients from one segment to the next are extremely low (a few centimetres of water only) with the result that gravity plays a very important part in the normal emptying mechanism from the renal pelvis For example if we try to perform excretion pyelography with the patient in the standing position there will be insufficient contrast medium in the pelvis to give any useful information in most cases In fact the renal pelves are practically empty at all times in most people when they are standing up The very low pressure differentials can explain many of the otherwise anomalous changes seen during the radiological study of the tract, especially under the X-ray intensifier

A mild transitory cysto-urethritis will increase the tone or œdema of the uretero-vesical orifice and may cause slightly delayed emptying of the whole ureter, although it will be impossible to detect any "obstruction" with a ureteric catheter In the same way the renal pelvis may distend quite considerably with only minor changes in hydrostatic pressure, while the calyces are continually altering their size and shape, not only because of their own muscular force, but because of the regurgitation of fluid from the contracting pelvis (Hanley 1959)

The importance of these observations lies in the fact that the pelvic size and shape can be easily altered in some people by changes of posture and urine volume, both of which are physiological factors, quite apart from extrinsic pressures which can be regarded as pathological factors The reason why some individuals are more susceptible to these changes than others may well be a simple variation of the normal anatomy A review of many thousands of routine pyelograms shows that very few renal pelves are alike in size or shape, or in their movement patterns, and that the "normal" covers a very wide range, extending from a funnel pelvis without any obvious pelvi-ureteric junction at one extreme, to a rounded pelvis with a well marked tonically closed junction at the other (see figure)

The funnel pelvis is by far the commonest type It will empty completely in the standing position and is hardly affected at all even by extreme diuresis, any excess of fluid merely escaping through the wide-open junction into the upper ureter

At the other extreme, the *rounded pelvis* has a tonically closed junction, and may retain small quantities of fluid even in the upright position It is very sensitive to changes in urine volume and may enlarge quite considerably during periods of diuresis

The upper ureteric segment just below the pelvis is rarely defined radiologically and contains urine only when the junction opens to discharge its contents

These anatomical variations may well explain the development of a hydronephrosis in some instances One would not expect a wide-open funnel pelvis to become hydronephrotic On the other hand, a full rounded pelvis with a tonic junction may well become overdistended and turn into a true clinical hydronephrosis (fig D) These assumptions have been confirmed during the surgical exploration of nearly 200 hydronephroses When all the adhesions and bands and vessels had been cleared away, a smooth funnel junction which emptied freely and rapidly was found in less than 8% of the cases The great majority showed a typical rounded pelvis with a clear-cut pelvi-ureteric junction and a relatively high insertion Distension of the pelvis with saline produced active contractions, but these nearly always hesitated or stopped completely at the pelvi-ureteric junction and did not continue on smoothly into the upper ureter

These clinical observations accord with Murnaghan's (1958) finding that there was an alteration in the arrangement of the muscle fibres at the junction in many hydronephroses, compared with the normal funnel-type pelves

Development of Hydronephrosis

It seems that true intrinsic strictures of the pelvi-ureteric junction are either congenital, in which case they produce a hydronephroses in childhood, or acquired due to inflammation or trauma, in which case they can cause trouble at any age The youngest congenital example in this series was in a baby one day old, by which time the parenchyma was already destroyed

Apart from children or adults with a long history of infection, however, a true mechanical narrowing of the lumen is very rare, and in the great majority of cases a bougie can be passed through the junction easily in both directions once the extrinsic adhesions have been freed Unfortunately the fact that the lumen will admit a bougie does not necessarily mean that it will allow urine to pass freely, and this is a fundamental point in the ætiology of hydronephrosis Even after the most meticulous ureterolysis, a majority of hydronephroses will be found to have this rounded full pelvis with a tonic junction which prevents the spontaneous escape of urine Pelvic contractions may be very active but they stop short at the junction, and only an occasional wave passes on into the the ureter Such a pelvis can certainly be made to empty easily by slight digital pressure, but it does not seem to be able to develop this slight increase in pressure by its own muscular contractions For the purposes of treatment this is a vital observation, because having removed all vessels and bands from the region of the pelvi-ureteric junction we are still left with some anatomical factor as the primary cause of the distended pelvis, and this may well be a "tonic" junction

Intermittent Hydronephrosis

The phenomenon of renal pain associated with an excessive diuresis is now becoming recognised by urologists as a definite clinical entity (Clarke 1959), and in this review we have encountered 6 proven examples of intermittent hydronephrosis Excretion pyelograms performed on these patients after routine dehydration did not show any gross dilatation, but when the examination was repeated and they were given copious fluids to drink after the exposure of the five-minute film, a marked pelvic distension was seen within fifteen to thirty minutes Without exception these pelves were of the rounded or full type with a tonic closed junction It must be re-emphasised that in most cases this rounded pelvis with a tonic junction is perfectly consistent with normal renal function and is symptomless The dividing line, however, between a rounded pelvis with a tonic junction and one with a hypertonic junction producing a true hydronephrosis is hard to define (see figure) Several of the patients with hydronephroses in this review gave a history indicating that they had had intermittent attacks of distension for a varying length of time—often for years—before the condition finally became irreversible

Various factors may precipitate this final irreversible state, but it is easy to imagine that if a patient with intermittent dilatation of the pelvis also has awkwardly placed vessels or fibrous condensations of the fascia, the pelvi-ureteric junction could eventually prolapse through a vascular window, and once there it could not escape back again

Age-incidence

Since this tonic junction is obviously present at birth it is interesting to speculate why a majority of "clinical" hydronephroses are not detected until adult life Over half of the 180 conservative operations for hydronephrosis in this series were performed on young soldiers whose average age was 24, with a preponderance in the 18–19-year-old groups, and it is interesting to note that the average age of the civilian patients operated upon at St Paul's or at Hillingdon Hospital was six years older than this (30 years) One possible explanation of this finding is that although both groups of patients had some potential cause for a hydronephrosis in their pelvi-ureteric junctions, some factor associated with military life drew attention to the fact earlier than would normally have been so A very interesting feature in support of this theory was the large number of young soldiers who volunteered or admitted the information that their loin pain was precipitated or made worse by copious fluids, whereas this was not such a common finding in the older civilian group There is certainly little doubt that many National Servicemen were subjected to strenuous exercise for the first time in their lives and therefore drank large volumes of fluid at irregular intervals, and some acquire a taste for beer

Diagnosis

The diagnosis of hydronephrosis can nearly always be made by excretion pyelography, and the phrase "non-functioning hydronephrosis" should be used with caution In our experience "non-function" is a very unusual finding and there are very few hydronephroses which will not show some radiological shadow on a delayed film taken two to three hours after the injection of one of the newer "tri-iodine" contrast media In fact, if a retrograde pyelogram is necessary to make the diagnosis, the kidney probably really is non-functioning and will have to be removed A ureteric catheter must, however, always be passed immediately before operation to exclude disease of the bladder neck or ureter not revealed by the excretion pyelogram In this series 3 mega-ureters, 1 ureteric calculus, and 2 primary carcinomas of the ureter (both under 25 years of age) were detected immediately before operation by this means

Retrograde Pyelography a Warning

The strongest warning should be given against the use of retrograde pyelography by the surgeon who is not prepared to carry on in the very near future (twenty-four hours at most) and perform a plastic procedure if necessary If there is even a remote chance that the patient will require transfer to another centre, or that operation will not be possible immediately, there is absolutely no justification for passing a ureteric catheter It is not necessary for the diagnosis and may well destroy the kidney within a few hours The danger is seldom due to the introduction of infection, but rather to the resultant overdistension which may prove the last straw and upset the equilibrium between urinary excretion, reabsorption, and escape through the junction Even if the pelvis is carefully emptied by aspiration through the catheter after the X-ray is completed, the mere passage of the catheter will increase the œdema of the junction and may precipitate complete retention, in the same way that bladder retention can occur after catheterisation or cystoscopy in a man of prostatic age We have seen 7 hydronephroses which were immeasurably damaged by a failure to observe this rule, and 2 were completely destroyed One patient began to have rigors during a flight home from foreign parts, and a rapid nephrectomy revealed a widespread pyelonephritis with multiple abscesses throughout the parenchyma The urine was known to have been sterile less than seventy-two hours previously

Surgery

Indications

Patients are often referred to the urologist with an excretion pyelogram showing a full rounded pelvis on one or perhaps both sides, and it is sometimes difficult to convince the patient and his doctors that the condition is within normal limits, and that " back pains " are infinitely more common than hydronephroses Certain data are necessary, however, before one can say with reasonable certainty that a full rounded pelvis has not progressed beyond the limits of the normal range, and the emptying efficiency rather than the emptying rate is the most important single factor A pelvis which is still shown as " filled " at the end of an hour in a dehydrated patient is not necessarily pathological unless it fails to empty in the upright position It may simply be a "rounded pelvis with a tonic junction" If the contrast medium is not rapidly washed out by diuresis, and certainly if the pelvis increases greatly in size, it is most probably pathological

As a general rule, by the time a hydronephrosis has produced sufficient symptoms to draw attention to itself, it has reached an irreversible and therefore a progressive state and should be treated by conservative surgery The full rounded pelvis which is only moderately distended, however, presents the most difficult choice In the absence of symptoms or where the discomfort is only of very recent onset, one should be patient and review the case in a few months' time On the other hand, a long history of loin pain or of repeated short attacks, particularly if they are precipitated by a large fluid intake, should call for surgery Such symptoms become worse not better, and the disease progresses steadily

The long-term review of this series indicates that it is well worth trying to preserve the great majority of hydronephroses in young adults, and that any surgical exploration should be designed for conservative surgery rather than for nephrectomy

In spite of the radiological appearances, and of the results of elaborate renal-function tests, the most important point in prognosis is the thickness of the renal parenchyma found at operation, and this may be quite unrelated to the size of the sac

Choice of Operation

The series consists of well over 200 cases of hydr nephrosis, 181 of which have been treated by conservati surgery A Davis (1943) intubation type of operation w performed 69 times The size of this group is due to t inclusion of many of the early cases where a splint w left in situ after a simple ureterolysis or a resection of t pelvis to avoid obstructing vessels, but where a true plas operation at the junction was deemed unnecessary becau there was no true intrinsic stricture I would now perfo a Foley (1937) or Culp (1951) on every " tonic " junctio The next largest group were those patients who had so form of incision through the junction followed by a fl closure (Foley 34, Culp 32) A simple ureterolysis witho opening the pelvis was performed 10 times, and was co bined with a pedicle sympathectomy on 8 occasions The were 3 Hamilton-Stewart (1947) and 4 Priestley (193 operations The common factor in these 153 operatio was the maintenance of anatomical continuity betwe pelvis and ureter

The remaining 29 cases were treated by some form operation which resected the pelvi-ureteric junction a joined the ureter to the pelvis at its most dependent poi Anderson and Hynes (1949) 16, von Lichtenburg (1929) Kuster (1892) 4, Lubash and Madrid (1937) 3

The introduction of the X-ray image intensifier (Hanl 1959) has been of inestimable value to us in the study hydronephrosis, not only before operation as a guide prognosis but also postoperatively when the function results of different types of plastic procedures have bee compared and studied in conjunction with the anatom encountered In general, the long-term results aft operations where continuity between pelvis and ureter wa preserved have been infinitely better than those in whic complete resection and re-anastomosis was carried out A observed on the intensifier screen the best emptying move ments were seen after the Foley or Culp operations, an these have now become our operations of choice

Nevertheless the intubated ureterostomy operation (Davis) have been clinically satisfactory, especially sinc they have been used in many of the most difficult cases such as those with tight junctions associated with intra renal pelves, and in 11 cases operated on for the secon time Although the newly formed segment tends t behave as a rigid tube when viewed under the intensifier drainage is adequate and not one secondary nephrectom has been necessary This may not be such an æsthetic operation to perform, but it is a simple and safe procedur and is invaluable when in difficulties

The type of operation performed, however, is probably of no great importance provided that there is an oblique (not a circular) scar, and that a " tonic junction " is converted into a wide-open " funnel junction " opening into normal ureter, by any technique preferred by the surgeon concerned In principle, if a careful ureterolysis reveals a wide-open funnel junction over which waves pass smoothly into the ureter (and this is a rare finding), there will be no need for a plastic operation on the junction, although the pelvis may require resecting to overcome a high insertion or awkwardly placed vessels When a tonic junction is found, as it will be in most cases, some form of refashioning to convert it into a funnel will be necessary if consistently satisfactory results are to be achieved

Long-term Results

16 patients underwent successful bilateral operations, 11 were operated upon with success for a second, or even

, third time, and 9 women subsequently had 1 or more hildren without any urological complications

No case of hypertension developing after a plastic peration has been recorded, though several patients xperienced a slight but temporary drop in blood-pressure fter operation

Just over 72% of the 181 plastic operations have been raced The most comprehensive review has been ossible in the Service personnel, where "ability to serve" an be assessed much more objectively than merely asking he patient how he feels

It is most encouraging to note that less than 12% of the men (including 6 with bilateral disease) were discharged on medical grounds, the remainder being able to complete their National, short, or full-time Service 21 men are at present still serving, 16 of them in category P2 (FE) and five as P5

A follow-up of those who have since left the Army shows that 4 of them subsequently had a nephrectomy performed elsewhere An analysis of these 4 is instructive 2 had pain and urinary infection, but the other 2 were symptom-free and uninfected though they still had radiological evidence of a dilated pelvis It is doubtful whether nephrectomy was necessary This last point emphasises the fact that success after a conservative operation for hydronephrosis is not measured by radiological changes in the pelvic outline, though improvement in this respect is always gratifying

Success consists of (*a*) relief of pain, (*b*) relief of infection, and (*c*) arrest of the progress of the condition.

The most important point to emerge from this series dating back over twenty years is that in spite of the pessimistic outlook of many surgeons, conservative surgery is nearly always well worth while and that relatively few hydronephroses really require removing

I wish to thank the Director-General, Army Medical Services, Lieut -General Sir Alexander Drummond, for his kind permission to include the Service cases in this review, and also Colonel A. G D Whyte, reader in surgery at the R.A.M C College, for his great help in tracing the patients

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"Where the scientist begins to head for confusion is when, like Humpty Dumpty, he takes perfectly ordinary words and tries to make them mean not what he has been taught at school they *do* mean but what he *wants* them to mean The physicist says 'hot', not when he means hot but when he means radio-active, and he is aggrieved at not being understood. Soon, by imperceptible steps, the stage is reached when one kind of scientist uses a word to mean one thing and another kind of scientist uses the same word to mean something quite different. For example, to a biologist 'plasma' is the liquid in which the blood corpuscles are suspended, but to a physicist 'plasma' is electrified gas And so the different kinds of scientists grow away from each other just like prehistoric tribes which once shared the same grunts and clicks but which, as the areas they occupy separate, do so no longer"—MAGNUS PYKE. *Listener*, Sept. 8, 1960, p 380

ATHEROSCLEROSIS AND BETA-GLUCURONIDASE

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ATHEROSCLEROSIS is a disease caused by metabolic changes Disorders of lipid metabolism have been especially incriminated.

The thyroid (Dauber et al 1949) and œstrogenic (Pick et al 1951) hormones, which have been shown to lower the high plasma-cholesterol levels associated with atherosclerosis, are known to increase the β-glucuronidase activity (Fishman and Fishman 1944, Fishman et al 1950, Pittoni and Barbieri 1953) Similarly heparin, used to lower the plasma-cholesterol level, also raises the serum-β-glucuronidase activity (Kayahan and Demiroglu 1959) The serum-β-glucuronidase activity of animals which are unsuitable for studying experimental atherosclerosis is much higher than that of those which are suitable for this purpose For example, as a mean value, the serum-β-glucuronidase activity of cats is 10,000 units per 100 ml, of chickens 1820, of rabbits 1850 (Kayahan and Akçasu 1959) For these reasons, the role of β-glucuronidase in the pathogenesis of athersclerosis has been investigated.

Animal Experiments

40 two-week-old chickens were studied

These chickens were divided into four groups of 10 The first group was fed with commercial chicken mash The second and third groups were both given commercial mash with 2% cholesterol and 5% cotton-seed oil for ten weeks, and the third group was also given 500 units daily β-glucuronidase by injection. The fourth group had the same diet as the second and third groups for six weeks, and then, in addition, β-glucuronidase 800 units was injected daily for four more weeks At the end of ten weeks all the chickens were killed, and the β-glucuronidase activity, total-lipid, and total-cholesterol of their serum were estimated. In addition, the aortas were removed and examined for atherosclerotic lesions To evaluate the aortic lesions quantitatively, the grading method of Horlick and Katz (1949) was used. The β-glucuronidase activity of the serum was determined by the method of Talalay et al. (1946)

TABLE I—THE EFFECT OF β-GLUCURONIDASE IN CHOLESTEROL-FED CHICKENS

Experimental groups	Degree of aortic atherosclerosis	Serum-total-lipid (mg per 100 ml.)	Serum-cholesterol (mg per 100 ml.)	Serum-β-glucuronidase activity (units per 100 ml.)
1	0	242–386 *(306)*	90–115 *(102)*	1230–2880 *(1820)*
2	0·7–2·8* (2·1)	3238–6226 *(4854)*	850–1420 *(1185)*	750–1420 *(890)*
3	0–1 *(0·1)*	722–986 *(824)*	420–685 *(575)*	1340–3250 *(2320)*
4	0·2–1·2 *(0·5)*	1326–2435 *(1862)*	660–930 *(785)*	1290–3120 *(2130)*

* The figures give the range of values, the averages are in parentheses

Results

The effect of β-glucuronidase on cholesterolæmia, lipæmia, serum-β-glucuronidase levels, and aortic atherosclerosis is shown in table I

Conclusions

Feeding with cholesterol decreased the serum-β-glucuronidase activity in the second group of chickens The severity and grade of aortic atherosclerosis were lower in the third and fourth groups than in the second group The serum-cholesterol levels of the third and fourth groups did not rise as much as those of the second group The serum-β-glucuronidase activity was increased when this enzyme was administered

These findings suggest that β-glucuronidase has a preventive and probably a therapeutic effect on experimental atherosclerosis

Observations on Patients with Atherosclerosis

Three different investigations were made

1 The β-glucuronidase activity of the serum was estimated in 20 normal and 20 atherosclerotic patients

2 The β-glucuronidase activity of the intima was determined in 10 normal and 10 atherosclerotic human aortas The intima of the normal aorta and of the atherosclerotic lession was dissected, and the enzyme activity per gramme of tissue was estimated in the homogenate prepared from them

3 The effect of β-glucuronidase on the serum-lipids and on the clinical manifestations of atherosclerosis was studied in 10 atherosclerotic patients β-glucuronidase 25,000 units daily was injected intramuscularly for fifteen days, and after that the same amount was given weekly for two more weeks

The patients chosen for the third study were

CASE 1 —A man of 48, with retrosternal pain on exertion for three years

CASE 2 —A man of 50 with precordial pain on exertion for three months, and an anterior myocardial infarction ten days before admission to the clinic, was treated only with β-glucuronidase

CASE 3 —A woman, aged 58, with intermittent claudication in her left leg for two years, and retrosternal pain on exertion for three years About six weeks before admission to hospital a small ulcer appeared on her left 5th toe The dorsalis pedis, posterior tibial, and polpiteal arteries were not palpable on the left

CASE 4 —A 60-year-old man, with mild diabetes for fifteen years, and retrosternal pain on exertion for three years

CASE 5 —A man of 63, with a duodenal ulcer and precordial pain on exertion for three years

CASE 6 —A 63-year-old man, with mild diabetes for nine years, and retrosternal pain on exertion for eight years

CASE 7 —A man, aged 65, with retrosternal pain on exertion for six years

CASE 8 —A man of 68, with precordial pain on exertion for four years

CASE 9 —A 70-year-old man, with intermittent claudication in his right leg for three years, and retrosternal pain on exertion and at rest for six months Four months previously he had had a posterior myocardial infarction A small patch of gangrene developed on his right 5th toe a month before admission to the clinic The dorsalis pedis, posterior tibial, and popliteal arteries were not palpable on the right The minute blood-volume, measured by plethysmography, was 0 1 ml in this foot (normal value 4–6 ml)

CASE 10 —A man of 85, with mild diabetes for eighteen years, and retrosternal pain on exertion and intermittent claudication in both legs for two years The dorsalis pedis, posterior tibial, and popliteal arteries were not palpable on either side The minute blood-volume was 0 6 ml in each foot In all these cases, electrocardiograms taken at rest showed positive signs of coronary insufficiency

I studied the effect of β-glucuronidase on total lipæmia, total cholesterolæmia, coagulability of the blood, electrocardiographic signs, electrophoretic properties of the serum-lipids, serum-β-glucuronidase level, and on their symptoms

The β-glucuronidase activity was estimated as before

α and β lipoproteins of the serum were examined by paper electrophoresis, using Whatman no 31 paper and barbitone sodium buffer at pH 8 6, the paper was stained with Sudan black, and the β/α lipoprotein ratio was calculated

The coagulability of the blood was determined by the heparin-tolerance test Oxalated blood from the patient and from a normal subject was centrifuged to separate the plasm After recalcification of the plasma 1 unit of heparin was adde to 0 5 ml of this plasma, and then the coagulation-time w measured From these values the following index was ca culated

TABLE II—β-GLUCURONIDASE ACTIVITY OF THE SERUM AND INTI

Subjects	Serum-β-glucuronidase activity (units per 100 ml)	Aortas	β glucuronidas activity of aortic intima (units per g)
20 normal cases	750–1250 (Average *980*)	10 normal intimas	12 9–16 6 (average *14 2*)
20 atherosclerotic patients	360–830 (average *620*)	10 atherosclerotic intimas	0–5 7 (average *2 3*)

$$\frac{\text{Heparin tolerance of patient}}{\text{Heparin tolerance of normal subject}} \times 100 = \text{Index}$$

A value lower than 100 indicates hypercoagulability, and high than 100 indicates hypocoagulability (Kaulla 1953)

Results

The results of the first and second investigations ar shown in table II, and those of the third investigation i table III

Conclusion

The finding that β-glucuronidase activity in the serun of atherosclerotic patients and in atherosclerotic intimas i lower than that found in normals suggests a correlation between atherogenesis and β-glucuronidase Under th influence of β-glucuronidase the total lipæmia, the total cholesterolæmia, and the lipid bound to β-globulin all decreased, while the lipid bound to α-globulin and the serum-β-glucuronidase activity increased in every patient.

TABLE III—EFFECT OF β-GLUCURONIDASE ON SERUM-LIPIDS, SERUM β GLUCURONIDASE ACTIVITY, AND BLOOD COAGULABILITY

Cases	Serum-β-glucuronidase activity (units per 100 ml)		Total lipæmia (mg per 100 ml)		Total cholesterolæmia (mg per 100 ml)		β/α lipoprotein		Coagula bility index	
	B*	A†	B	A	B	A	B	A	B	A
1	360	420	969	593	310	175	7 8	5 14	66	103
2	474	574	1250	625	270	150	12	6 44	62	107
3	462	528	1218	781	330	200	7 3	4 28	72	115
4	378	515	1500	860	360	220	13 1	8 15	60	113
5	586	682	906	750	240	200	9 14	6 87	74	117
6	715	825	1247	920	285	200	11 5	7 49	59	106
7	826	848	1285	758	325	175	12 3	6 47	64	122
8	472	508	1382	768	345	185	10 9	7 12	67	109
9	386	415	912	656	220	165	8 64	4 78	63	118
10	524	562	750	652	250	150	9 82	5 47	68	111

* B =before treatment. † A =after treatment

The heparin tolerance test revealed hypercoagulability of the blood in these patients at first, but with β-glucuronidase treatment the blood became hypocoagulable

All 10 patients improved clinically The precordial pain on exertion disappeared in the first 8 cases, and the electrocardiograms in 5 cases returned to normal The necrosis of the toes in cases 3 and 9 completely healed in twenty days, and the walking capacity of cases 3, 9, and 10 had increased considerably at the end of treatment. In cases 9 and 10 the minute blood-volume of the foot was only very slightly raised, and the arterial pulsations of the legs did not change, but the rapid healing suggests that β-glucuronidase increased the cell proliferation and tissue regeneration

Discussion

Levvy et al (1948) suggested the role of β-glucuronidase in tissue regeneration, and its topical application has cured diabetic and varicose ulceration very quickly (Kayahan 1959) This also shows that β-glucuronidase promotes tissue regeneration and protein synthesis

The present results suggest that β-glucuronidase is an nzyme which has a profound effect on the metabolism of pids and also on the metabolism of proteins—both of hich contribute to the development of atherosclerosis hen altered. Thus an enzyme defect—the defect of -glucuronidase—may play a part in the pathogenesis of therosclerosis, and β-glucuronidase may have a thera- eutic effect.

I am grateful to Prof Senat Tavat, head of the department, for his terest and encouragement in this work.

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BLOOD-VOLUME AND TOLERANCE TO PENTOLINIUM IN THE TREATMENT OF HYPERTENSION

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WHEN bisquaternary ganglion-blocking agents are given in cases of arterial hypertension, tolerance to the drug will ordinarily develop in the course of days or weeks This increasing tolerance is especially significant for hexamethonium and some other earlier compounds, such as pentamethonium and hexamethylene-bis-dimethylethyl ammonium bromide (Smirk 1952) With more recent drugs like pentolinium ('Ansolysen') and mecamylamine ('Inversine') tolerance will also increase, but to a lesser degree than with hexamethonium (Smirk 1953, 1957, Freis et al. 1954)

Retention of salt and water during treatment with hexamethonium or pentolinium has been described (Fraser and Lowe 1954, Rønnov-Jessen 1954, 1955) This is sometimes followed by a considerable fall in the hæmoglobin level, which corresponds to an increase of the blood-volume. In 1954 I observed in some cases an increase in tolerance to pentolinium together with salt and water retention. When the surplus salt was excreted, the original tolerance was re-established. But the possibility that the increase of tolerance is due to retention of salt and water was not confirmed in a bigger series of patients

For many years it has been known that a diet poor in salt enhances the hypotensive effect of ganglion-blocking compounds (Smirk and Alstad 1951, Smirk 1953, Freis et al. 1954) The same effect has been observed with mercurial diuretics.

Recently many observations on the potentiating effect of chlorothiazide on ganglion-blocking agents have been reported. Tapia et al. (1957), Freis et al. (1958), Dustan et al. (1959), and Dollery et al. (1959) all found that when hypertensive patients were treated with chlorothiazide the plasma-volume decreased, and they assumed that this is the most important reason for the decrease of tolerance for ganglion-blocking compounds Dollery et al have proved that the sensitivity to pentolinium will decrease again when the diminished blood-volume is corrected with dextran devoid of salt.

These findings conform with the experience of Freis et al. (1951), who found that in hypertensive patients treated with hexamethonium even a small quantity—i.e., a few hundred millilitres—of blood removed by venesection often caused a significant fall in blood-pressure. This fall was promptly counteracted by reinfusion of the blood.

The changes in sensitivity during treatment with pentolinium seem to be mostly due to variations in the blood-volume.

The Study

Eight ambulant patients were studied, all with severe fixed hypertension but without uncompensated heart-disease. During the study the patients had a low-salt diet, but they were given additional salt—sodium chloride 4 g daily—to ensure a constant salt intake (a total of 5–5·5 g sodium chloride daily)

The patients were first given pentolinium alone for a few days, and then both pentolinium and a drug of the chlorothiazide group We measured repeatedly the blood-volume of the patients, and their concurrent sensitivity to pentolinium, before and during the drug trials.

Blood-volume

Blood-volume was determined by means of hexavalent radioactive sodium chromate (^{51}Cr) The red blood-cells of the patients were marked in vitro, and washed twice in physiological sodium chloride. The marked erythrocytes were injected intravenously as a 20 ml suspension of physiological sodium chloride after samples have been taken for standard comparison. 15–20 minutes later venous blood was taken without stasis, using dried heparin as an anticoagulant. Hæmolysis was produced by cooling below 20°C, and the activities of standard and hæmolysed blood samples were measured in a well-type scintillation counter

The blood-volume itself was calculated as the ratio between injected activity and activity per millilitre of blood. If another determination of blood-volume was made before the activity of the first injection had disappeared, the volume was worked out from the ratio between the last injection of active suspension and the increase of activity per millilitre of blood. The calculation was always tested twice, and counting was continued until the statistical error was less than 2%

The reliability of this method was checked by making two blood-volume determinations on each of ten patients within 45 minutes. The difference between the two varied from 1·2 to 6·3%, with an average of 3·7%

Sensitivity to Pentolinium

Variations in the sensitivity to pentolinium were shown by giving the same test dose of the drug intravenously before, and several times during, the treatment. The test doses, injected at least 12 hours after the previous dose of pentolinium, ranged from 1 to 3·5 mg of pentolinium bitartrate.

Before the injection the blood-pressure was measured with the patient erect and lying down every 2nd minute until three consecutive results were constant. After the injection

TABLE I—BLOOD-VOLUME AND WEIGHT BEFORE AND AFTER 3–8 DAYS' TREATMENT WITH PENTOLINIUM

Case no.	Date	Blood-volume (ml.)		Difference (%)	Weight (kg.)		Difference (%)
		Before	After		Before	After	
1	Sept. 22 „ 26	2750	3280	−19·3	37·7	39·0	−3·4
2	Aug. 28 Sept. 1	5150	5350	− 3·9	80·3	80·1	−0·2
3	July 21 „ 27	3610	3760	− 4·2	67·3	68·5	−1·8
4	Dec. 16 „ 20	3500	3770	− 7·7	82·8	83·1	−0·4
5	Oct. 14 „ 19	4790	4320	− 9·8	72·8	72·2	−0·8
6	Feb 16 „ 24	4130	3930	− 4·8	73·6	73·1	−0·7
7	Nov 18 „ 21	4470	4940	−10·4	85·2	85·6	−0·5
8	Oct. 23 „ 28	4490	4550	− 1·3	83·1	82·4	−0·8

TABLE II—RELATION BETWEEN BLOOD-VOLUME AND SENSITIVITY TO PENTOLINIUM

Case no	—	Before treatment	During treatment with pentolinium	After 3–9 days' treatment with pentolinium and chlorothiazide or hydrochloro-*thiazide*	After blood-volume was corrected with 6% salt-free dextran
1	Blood-volume (ml) Reduction in M B P *	2750 17	3280 10	2830 21	
2	Blood volume (ml) Reduction in M B P	5150 17	5340 6	4670 22	
3	Blood-volume (ml) Reduction in M B P	3610 40	3760 30	3220 48	3700 31
4	Blood-volume (ml) Reduction in M B P	3500 40	3770 31	3120 ?†	3610 42
5	Blood-volume (ml) Reduction in M B P	4790 32	4320 56	4110 50‡	
6	Blood-volume (ml) Reduction in M B P	4130 29	3930 32	3750 56	

* M B P = mean blood pressure (mm Hg) in the erect position

† During hydrochlorothiazide therapy the blood pressure decreased so much that it was impossible to complete the sensitivity test

‡ Because of the greatly increased sensitivity to pentolinium the third test dose was reduced to two-thirds of the previous ones

the blood-pressure was measured every 3–5 minutes for half an hour (8 times) with the patient in the same positions as before The greatest fall in the mean blood-pressure in the erect position was used as a measure for sensitivity to pentolinium The fall of blood-pressure when the patient was lying down was too inconstant for one to draw any conclusions about variations in sensitivity

The mean blood-pressure was calculated from the diastolic pressure plus a third of the pulse pressure The measurements were made with a standard mercury sphygmomanometer

Results

Table I shows the variations in blood-volume and body-weight during pentolinium treatment The blood-volume of six patients increased while that of two decreased The body-weight variations were negligible.

Tables II and III show the relation between blood-volume and sensitivity to pentolinium in the eight patients at different stages of treatment In the six with increasing blood-volumes the sensitivity decreased (cases 1–4, 7, and 8) In the two with decreasing blood-volumes the sensitivity to pentolinium increased (cases 5 and 6) In two patients (cases 7 and 8) the volume again fell during continued pentolinium treatment, and at the same time the sensitivity to the drug increased

In six cases the investigations were resumed after some days of combined treatment with pentolinium and chlorothiazide or hydrochlorothiazide In five the blood-volume decreased and the sensitivity to pentolinium increased, in one case so much that the test dose of pentolinium had to be reduced by one-third (case 5) In the last patient (case 4) the decrease of blood-volume was also significant, at the same time her blood-pressure became almost normal in the erect position, and a test dose of pentolinium was not given.

TABLE III—RELATION BETWEEN BLOOD-VOLUME AND SENSITIVITY TO PENTOLINIUM

Case no	—	Before treatment	During treatment with pentolinium		During prolonged combined treatment with pentolinium and hydrochloro-thiazide
7	Blood-volume (ml) Reduction in M B P	4170 35	After 3 days 4910 19	After 13 days 4680 34	After 72 days 4150 42
8	Blood volume (ml) Reduction in M B P	4190 43	After 5 days 4550 41	After 11 days 4260 18	After 81 days; 4630 46

Both in this patient and in another (cases 3 and 4) the *sensitivity was tested after correction of the reduced* blood-volume to about the original level by infusion of a 6% salt-free solution of dextran The sensitivity was almost the same as before treatment was begun

In two patients (table III) the investigations were repeated after about $2^1/_2$ months' treatment with hydrochlorothiazide and pentolinium In case 7 the blood-volume at the last measurement was nearly the same as before treatment, while the sensitivity to pentolinium had increased In case 8 the blood-volume increased by about 3% while the sensitivity was almost unchanged.

Discussion

The relation between blood-volume and sensitivity to pentolinium in this study indicates that the initial increase in tolerance for pentolinium and the increased sensitivity when chlorothiazide is given concurrently are due respectively to an increase and decrease in blood-volume An increasing tolerance has only been seen when the blood-volume has increased at the same time

This study shows, like those of Dollery et al (1959), that when the blood-volume, reduced by treatment with chlorothiazide, is restored by means of dextran devoid of salt, the sensitivity to pentolinium falls to the original level. This indicates that the increased sensitivity to pentolinium during treatment with chlorothiazide is almost entirely due to reduction of blood-volume and not to reduction of salt and water—and this is always so if the treatment with chlorothiazide lasts for a few days only. At the same time the assumption that chlorothiazide has a specific anti-hypertensive effect is disproved

On the other hand Wilkins et al (1958) and Wilson and Freis (1959) have found that during prolonged therapy with chlorothiazide the blood-volume and the extracellular fluid will, in the course of a few months, return to normal without the blood-pressure increasing as much as before One cannot therefore exclude a specific hypotensive effect of chlorothiazide during long-continued treatment

As shown in the tables the sensitivity changes in some cases are greater than can be explained from the changes in blood-volume, but they are not greater than can be expected when the inaccuracies of determining the blood-volumes and blood-pressures are taken into consideration

We do not fully understand the relation between the blood-volume and sensitivity to pentolinium Dustan et al (1959) have shown, however, that during treatment of hypertension with chlorothiazide a compensatory increase in vasomotor tone will develop as in oligæmia from other causes, and maintain the hypertension This provides a reasonable explanation of why the effects of ganglion-blocking agents are enhanced Furthermore these workers found that after correcting the decreased blood-volume with dextran the peripheral resistance again declined—a sign of decrease in vasomotor tone following the increase of blood-volume

If these results are tenable, a theoretical explanation of the initial increase of tolerance during treatment with pentolinium could be

Because of the fall in blood-pressure following pentolinium therapy the blood-volume will increase When the blood-volume increases, the neurogenic component of blood-pressure regulation diminishes, and consequently the effect of pentolinium also decreases

Hence this study suggests that the vasomotor ganglia themselves do not develop tolerance to pentolinium, but that the apparent increase of tolerance is conditioned by the increase in blood-volume

This study also clarifies the relation between variations in blood-volume and the sensitivity of hypertensive patients to pentolinium only If the above theoretical explanation is correct, the same mechanisms must contribute to the development of tolerance in treatment with any ganglion-blocking drug If in addition tolerance to these drugs happened to develop in the vasomotor ganglia themselves, this could be investigated along the same lines as the ones followed in this study

The relatively small changes in tolerance during treatment with the newer ganglion-blocking compounds are presumably based primarily on an increase of blood-volume, as in pentolinium therapy Preliminary investigations suggest that this is so with the tertiary amine, pempidine tartrate The very great increase of tolerance during treatment with hexamethonium has not yet been fully explained, but this increase also seems to be conditioned by an increase of blood-volume (Rønnov-Jessen, to be published)

Conclusions

In treating hypertension with pentolinium there is usually some increase of blood-volume when the sensitivity to pentolinium decreases

During continued therapy with pentolinium and chlorothiazide derivatives blood-volume again decreases and the sensitivity to pentolinium increases

When the reduced blood-volume is corrected by means of dextran devoid of salt, the sensitivity to pentolinium will reach about the same stage as before treatment

In two patients treated with pentolinium and hydrochlorothiazide for about $2^1/_2$ months, the sensitivity to pentolinium also depended on the blood-volume

Thus when pentolinium is given the increase of tolerance is mainly due to an increase of blood-volume As in earlier investigations, the increase of sensitivity during treatment with chlorothiazide is conditioned by a reduction of blood-volume

The investigations of Dustan et al. (1959) suggest that the increase of sensitivity to ganglion-blocking agents caused by chlorothiazide depends on an increase of vasomotor tone concurrent with the reduction in blood-volume It seems reasonable to presume, therefore, that during treatment with pentolinium the vasomotor tone declines when the blood-volume increases

The present study shows that it is unlikely that the vasomotor ganglia themselves develop tolerance to pentolinium The apparent increase of tolerance is conditioned by an increase in blood-volume, which probably causes a decrease of vasomotor tone

May & Baker Ltd. supplied the pentolinium compounds

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ALLEVIATION OF POST-HERPETIC NEURALGIA

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MOST patients recover from herpes zoster with no ill effects apart from scarring of the skin A few—usually elderly—patients continue to have intractable and distressing pain in the affected area, in some of these cases the pain of the acute eruption persists unabated, while in others there is a free interval This post-herpetic neuralgia may improve spontaneously, but usually it lasts throughout life and causes severe and constant distress, if not despair

Although many treatments have been recommended, it is generally agreed that none is effective Even extensive neurosurgical procedures are unlikely to give relief, leucotomy itself is often ineffective

Russell and his colleagues (Russell et al 1957, Russell 1959) have claimed good results from the repeated percussion of the affected area with an electric vibrator This method was originally tried in some of my cases, but it was not helpful because the patients were so eager for relief that they soon began to injure their skin by injudicious percussion.

The mechanism of post-herpetic neuralgia is not understood, but it has been postulated that pain is experienced when abnormal patterns of nerve impulses reach the central nervous system (Gooddy 1957) In most cases there is evidence of defective innervation of the damaged skin, and it seemed reasonable to attempt to modify the pattern of nerve impulses travelling to the central nervous system by setting up fresh patterns The satisfactory use of skin-cooling sprays for the treatment of pain from other causes (Travell and Rinzler 1952) led me to test this method in post-herpetic neuralgia. The results in 16 cases are reported here

Method

At first the skin over the painful area was sprayed continuously at a range of 24 in with ethyl chloride for 30–60 seconds, taking care to move the spray slowly so that the skin did not freeze. It was later found that intermittent spraying for 5 seconds every half minute for 2 minutes was equally effective, and that much less skin damage resulted. When spraying the head it was only necessary to warn the patient to keep his eyes firmly closed. Application of silicone barrier cream or a prednisone spray relieved persistent redness and blistering of the skin even when spraying with ethyl chloride was continued.

Ethyl chloride, sprayed through a coarse nozzle, is very effective, but its use, especially by lay people, is attended by hazards due to its flammability, its general-anæsthetic activity, and the ease with which it may freeze and injure the skin.

It is essential to use a vigorous spray, and the ethyl-chloride spray, general-anæsthetic pack with long nozzle (Hedley, no 13) is the most suitable of those commercially available The local-anæsthetic pack, and the general-anæsthetic pack with short nozzle, give a very fine spray which is usually ineffective In most patients the first few applications of the spray cause severe pain and even distress, but the subsequent relief soon

DATA ON 16 CASES OF POST-HERPETIC NEURALGIA

Case no	Sex	Age (yr)	Site	Duration (yr)	Relief (mos)	Comment
Failures						
1	M	76	Lt trigem I	13	0	Alcohol injection gasserian ganglion
2	F	66	Rt T8–10	4	0	Deep X-ray
3	F	74	Rt T7	9	0	Dorsal rhizectomy
4	M	64	Rt trigem I	1 5	0	Itching only
Successes						
5	F	67	Lt trigem I	1 1	6	
6	F	73	Lt T11	4	12	Relapsed on L A P *
7	F	72	Rt occip	0 9	8	" Wonderfully better "
8	M	65	Rt trigem I, II	2	18	Needs repeated sprays
9	M	82	Rt trigem I	5	15	" A godsend "
10	F	69	Rt T12	2 5	21	" A world of good "
11	M	65	Lt T9	2	3	" Much better "
12	F	59	Rt T5–7	5	9	Relapsed on L A P *
13	M	64	Rt C4–7	6	3	"
14	F	72	Rt trigem I	2 5	3	"
15	F	86	Rt C5	6	12	
16	F	76	Rt T4	1	10	

* Local-anæsthetic pack.

makes the patient willing to undergo this initial temporary discomfort At the beginning of treatment patients are sprayed daily by the doctor, but once the patients, or their relatives, are familiar with the technique, they are instructed to continue the treatment at home It is best to try to " drive " the pain away by spraying whenever severe pain recurs Sometimes remission takes place only after two or three sprayings, but thereafter steadily increasing periods of relief ensue

The Patients

16 patients (6 men, 10 women) were studied (see accompanying table) Their ages ranged from 59 to 86 (mean 70 6) years Post-herpetic neuralgia involved the trunk in 9 and the head in 7, the duration of the condition ranged from 10 months to 13 years (mean 4 1 years)

Results

Successes

In 12 cases the pain was relieved satisfactorily 2 of these are now in remission and do not use the spray at all The others spray themselves or are sprayed by relatives whenever severe pain recurs, the intervals between spraying vary from daily to once or twice per week All these patients are delighted with their treatment and describe it in terms such as " a godsend ", " has done me a world of good ", " wonderfully better ", and " much better " Sometimes the gratitude of these people, relieved of the pain they had expected to persist indefinitely, has been embarrassing The duration of relief has varied from 3 months to 21 months (mean 10 0 months)

4 patients were found, on review after an interval of some months, to have abandoned the use of the spray on the ground that it was no longer effective In each case it was discovered that the patient had inadvertently been issued with a different kind of spray This was a local-anæsthetic pack which has a much more feeble impact than the general-anæsthetic pack When these 4 patients were supplied with the correct type of spray, further and persisting relief resulted Another patient was referred by the private doctor because the spray treatment was ineffective Here, too, it was found that the local-anæsthetic pack had been used, and on changing to the general-anæsthetic pack satisfactory relief was obtained

Failures

4 patients failed to obtain satisfactory relief and the treatment was abandoned

In 2 the neuralgia affected the head and in 2 the trunk The duration of neuralgia in these 4 patients was 13, 9, 4, and 1 5 years 1 patient had undergone dorsal rhizectomy 8 years before, 1 had undergone alcohol injection into the gasserian ganglion 7 years before, and 1 had received deep X-ray therapy to the spinal cord 4 years before, the 4th had not previously been treated

The 3 previously treated patients showed little response to the spray and this method was eventually abandoned No other form of treatment was found effective in these cases

In the 4th case an initial period of satisfactory relief was followed by relapse which was thought to be due possibly to emotional tension between the patient and his wife The spray was discontinued for some months, and when treatment was resumed by me satisfactory relief was not obtained It seemed likely that pain had in fact been abolished, but the patient complained so bitterly of persistent itching that the result was regarded as unsatisfactory

Illustrative Case-records

Case 5 —A woman, aged 67, had had post-herpetic neuralgia for 13 months in the area of the first division of the left trigeminal nerve This responded to mechanical vibration, but the skin was soon damaged Initial treatment with ethyl chloride gave 9 hours' relief from pain After once-daily spraying for a week relief for up to 72 hours or more was achieved She then remained well for 6 months without therapy, but the pain recurred after a severe emotional shock This was again relieved by the spray, and the patient has remained pain free with occasional sprayings ever since

Case 9 —A man, aged 82, had had post-herpetic neuralgia for 4 years, affecting the first division of the right trigeminal nerve He was in a neurosurgical ward, and the neurosurgeon had just written "The patient is complaining bitterly I shall try gasserian ganglion injection of alcohol but I am not hopeful" Spray treatment was given daily for the first week and then at intervals of 3–4 days whenever the pain recurred The patient lives in a hostel, and the spraying is carried out by the attendant in charge He has now been relieved from severe pain for 15 months and says " Lovely, wish I'd known about this before " He describes the treatment as " a godsend "

Case 10 —A woman, aged 69, had had post-herpetic neuralgia for $2^1/_2$ years, affecting right T12 and L1 dermatomes Nine treatments with electroconvulsion had no effect The first few spray treatments gave temporary and partial relief, and after 5 days the patient began to have increasing periods of complete relief for up to 12 hours Eventually the patient had only occasional pain and did not really need the spray but asked to have one to keep at home because, she said, " it did me the world of good "

Discussion

It has not proved possible to devise a satisfactory form of controlled trial for skin-cooling treatment of post-herpetic neuralgia The results described here indicate that the method is worth trying

None of these patients had had satisfactory relief from any previous therapy other than by percussion with an electric vibrator Percussion, however, is unsatisfactory because it is liable to damage the skin The spray technique is simple, harmless, and satisfactory It has the great advantage that it can be carried out at home by the patient, a relative, or the district nurse, hence there is no need for persistent pain to be endured between visits to the doctor

The mechanism by which the skin-cooling spray acts is uncertain, but it seems to be related to the intensity of afferent stimulation This is supported by the lack of response when less intensive types of spray, such as the local-anæsthetic pack, were used instead of the coarse-nozzled general-anæsthetic pack In this series of cases change to a milder type of spray has been the commonest cause of relapse The patients did not appreciate the significance of the change from one type of spray to another, and this affords evidence that the results of treatment were not due to suggestion In 3 cases a special mixture of 'Freon' in cans with a very strong spray * was substituted for ethyl chloride with satisfactory results This mixture is not flammable, is not a general anæsthetic, and is not liable to freeze the skin Such a preparation may prove more satisfactory for home use by non-medical persons

I suggest that the relief of pain by cooling the skin depends on adequate afferent stimulation, and it is thus simply an example of the old therapeutic measure of counter-irritation. In 3 of the patients who did not respond the afferent stimuli may have failed to reach the central nervous system because of damage to the peripheral-nerve pathways by previous treatment In post-herpetic neuralgia affecting the first division of the trigeminal nerve, such as was present in 4 of the successfully treated patients in this series, there is no evidence of the trigger areas or local muscular spasm postulated by Travell and Rinzler (1952)

Summary

Otherwise intractable post-herpetic neuralgia was treated by brief interrupted spraying of the affected area with ethyl chloride

Of 16 cases 4 failed to respond, but 12 were satisfactorily relieved of pain for 3 to 21 months

I am indebted to Dr D A Cahal for supervising the treatment of 3 of the patients, and Dr W A Bain, who first introduced me to the analgesic properties of cooling sprays, for his unfailing support and encouragement

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STERNOCLAVICULAR ARTHRITIS

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ALTHOUGH the sternoclavicular joints may be involved in polyarticular disorders—e g, rheumatoid arthritis (Rathcke 1937), osteoarthrosis (Buckler 1955), ankylosing spondylitis (Cruikshank 1951), and syphilitic arthropathy (Sundt 1948)—acute sternoclavicular arthritis as an apparently isolated lesion has received little attention

Cyriax (1956) has described the features of sprained sternoclavicular joint consequent upon a fall. He emphasised that subluxation of the sternal head of the clavicle secondary to a ruptured ligament was especially likely in osteoarthrotic joints or in those which had been the site of bacterial infection

Heine (1926) described degeneration of the cartilages of both sternoclavicular joints as an ageing process, but he regarded these changes as asymptomatic and commoner in men, and he thought they were not aggravated by trauma Langen (1934) also regarded degenerative changes in sternoclavicular joints as inevitable after the age of 40, and Zimmer (1939) suggested that they were due to constant movements and were therefore usually more pronounced on the right Westerman (1942) agreed that asymptomatic degenerative changes were common, but thought that symptoms could be provoked by heavy manual work, and that, in these cases, the right sternoclavicular joint was more liable to be involved

PRINCIPAL FINDINGS IN NINE PATIENTS WITH ACUTE STERNOCLAVICULAR ARTHRITIS

Case no	Sex	Age (yr)	Side involved	Immediate cause	Other clinical features	Response to local steroid injection
1	F	57	R	House cleaning	Heberden s nodes Cervical spondylosis Tennis elbow	Complete relief
2	F	49	L	Carrying ledgers	Osteoarthrosis of knees Heberden's nodes Hallux valgus	Complete relief
3	F	49	R	Carrying fruit trays	Osteoarthrosis of knees Heberden s nodes	Complete relief
4	F	52	R	Carrying books	Heberden s nodes Pericapsulitis of shoulder	Complete relief
5	F	54	R	Clipping a hedge	Osteoarthrosis of knees and trapeziometacarpal joints Lumbar spondylosis	Improved, then cured after 2nd injection
6	F	47	L	Floor polishing	Osteoarthrosis of knees Hallux valgus	Complete relief
7	M	63	L	Carrying steel girders	Spondylosis Osteoarthrosis of knees	Complete relief
8	M	63	R	Loading lorries	Lumbar spondylosis	Complete relief
9	F	57	R and L	Carrying trays of dishes	Epilepsy Tertiary syphilis	Not given. Responded to antisyphilitic therapy

Kowallik (1951) listed the features of painful and swollen osteoarthrotic sternoclavicular joints, and discussed their differential diagnosis from traumatic subluxation of the clavicle which, in his experience, was seen in young people only

Sokoloff and Gleason (1954) studied the sternoclavicular joints at necropsy in eighty-five cases, twenty-one of which had had symptoms in these joints during life. They described in detail the degenerative processes, and found that the synovial membrane was not significantly involved, but their studies did not include any case of acute or severe osteoarthrosis of these joints

Arlet and Ficat (1958) reported the case-histories of twelve women with osteoarthrosis including unilateral involvement of the sternoclavicular joint, eight of whom had presented with an isolated complaint of pain in this joint. These workers emphasised that the symptoms could be severe and chronic, and they had to resort to excision of the sternal head of the clavicle in two cases to relieve the intractable pain.

Between May, 1957, and March, 1958, nine patients—seven women and two men—presented at the casualty department of the Royal Victoria Infirmary with acute symptoms referable to one or both sternoclavicular joints, and they were later investigated in the department of physical medicine The clinical features are summarised in the table In cases 1–8 inclusive the following investigations were normal erythrocyte-sedimentation rate, blood Wassermann and Kahn reactions, gonococcal fixation test, Rose-Waaler test, full blood-counts, and urine analysis

Illustrative Case-reports

Case 3 —A widow of 49 started work in a factory in September, 1957 This entailed packing boxes of fruit and then carrying for several yards trays laden with these boxes (about 50 lb) about 8 or 10 times daily She began to have pain and swelling in the right sternoclavicular region which persisted for 4 weeks, and then slowly improved with rest. The symptoms recurred in November, and she finally gave up her work in December. After that she was well until March, 1959, when she took a job as an ironer in a laundry and was again troubled with pain and swelling in the right sternoclavicular region. This responded to an intraarticular injection of hydrocortisone acetate 50 mg., and has not recurred.

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* Specially prepared by Smith, Kline & French Laboratories, Philadelphia, U S.A, at the suggestion of Dr W A Bain, director of the Smith, Kline & French Research Institute, Welwyn Garden City, England

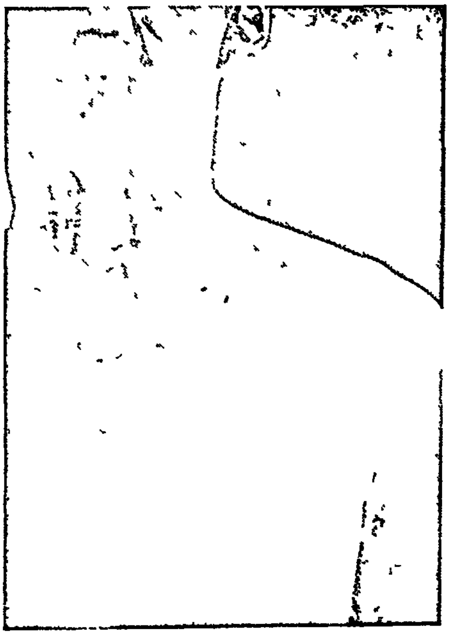
Examination revealed Heberden's nodes over the terminal phalanges of her hands, well-established osteoarthrotic changes in both knees, and subacute arthritis of the right sternoclavicular joint, with swelling, tenderness, and pain, and crepitus on movement. Radiographs showed mild osteoarthrotic changes of the right sternoclavicular joint, and undoubted osteoarthrotic changes in both knees. The lumbar spine, sacroiliac joints, and chest showed no significant abnormality.

Case 5.—A housewife, aged 54, had acute swelling and pain in the right sternoclavicular region in May, 1957, the day after mowing a lawn and clipping a hedge.

The physical signs suggested an acute sternoclavicular arthritis. Crepitus was elicited also in the left joint, which was symptom-free. She had osteoarthrotic changes in both knees and both trapeziometacarpal joints. Radiographs of the sternoclavicular joints were normal, but there was lumbar spondylosis and degeneration of the L5/S1 disc.

The patient was given an injection of hydrocortisone acetate 25 mg. into the right sternoclavicular joint, with much relief of symptoms. Her condition relapsed on Oct. 25 after exceptionally heavy housework, and her symptoms again responded to an injection of hydrocortisone acetate 25 mg. There has been no subsequent relapse.

Case 7.—A miner of 63, employed in fitting girders, had acute pain and swelling in the left sternoclavicular region in October, 1957, after a period of exceptionally heavy work. He carried the girders and held them in the left hand, imposing severe strain on the left arm and shoulder. Rest did not relieve his symptoms, and when he was referred to hospital on Nov. 16 he had signs of acute sternoclavicular arthritis on the left (see figure), and of cervical and lumbar spondylosis and osteoarthrosis of both knees. Radiographs showed moderate osteoarthrotic changes of the left sternoclavicular joint, and well-marked changes of cervical spondylosis.



The patient was given an injection of hydrocortisone acetate 50 mg. into the left sternoclavicular joint, and within 72 hours the pain was abolished and the swelling much reduced. He was able to return to work, and he has not relapsed.

Case 9.—A woman of 57, employed as a dishwasher, developed painful swelling in the left sternoclavicular region shortly after starting a new job where she had to carry heavy trays full of dishes. During the next 3 months she had similar symptoms and signs on the right, and she gave up her job. Her symptoms persisted despite rest, and she was referred to hospital in October, 1957, with bilateral signs of sternoclavicular arthritis, greater on the left. The swelling was firm, and was not an effusion. Radiographs of the sternoclavicular joints and spine were within normal limits. She had no other abnormal physical signs, but she had had occasional epileptic fits, well controlled by phenobarbitone, over 17 years.

The blood Wassermann reaction was strongly positive, and the diagnosis of syphilis was confirmed by a positive treponema-immobilisation test. The erythrocyte-sedimentation rate was normal. The patient was treated initially with potassium iodide gr. 15 t.d.s., and over 3 weeks the joint swellings regressed. With further antisyphilitic therapy improvement has been maintained.

Discussion

The condition described in the first eight cases is obviously not uncommon, since all these patients were seen at one hospital department within 9 months. But in no case had the diagnosis been established before the patient was sent to hospital. The clinical features of sternoclavicular arthritis were those of a synovitis and capsulitis, with various degrees of effusion. Crepitus, when elicited, was apparently superficial and in keeping with soft-tissue thickening. It was not the coarse grating crepitus found with bony and cartilaginous erosions. Most of these patients, however, all of whom were over 45, had evidence of osteoarthrotic changes elsewhere.

Acute sternoclavicular arthritis is clearly different from sternoclavicular subluxation, in which the sternal end of the clavicle is displaced, forming a hard bony projection. None of the present series showed any evidence of subluxation clinically or radiographically. Furthermore subluxation of the sternoclavicular joint in the elderly is often without symptoms, and in the young is usually due to severe trauma.

The factor which seemed to precipitate symptoms in all our cases was unusual or undue strain on the joint, associated with heavy work. Even in case 9, with syphilis, there was a history of trauma to the sternoclavicular joints. In the two patients who relapsed, further lifting strains were implicated, and, except for case 9, the three patients with acute signs in the left sternoclavicular joint had been doing work which threw special strain on the left arm and shoulder. The side involved in our series—five right, three left, and one bilateral—supports the findings of Zimmer (1939) and Westerman (1942), but the high female/male sex-ratio (7/2) is not in keeping with the pathological observations of Heine (1926) on sternoclavicular joints. A striking fact is that no fewer than five of the seven women in our series were obliged to work, and they had either recently started work or were undertaking some unaccustomed task. The clinical adage of shoulder pain being commoner in "widows who take in washing" can in a modified way apply to acute sternoclavicular arthritis.

Only one patient had an underlying disease (case 9), but this example shows the necessity for investigation of acute sternoclavicular arthritis. In the other patients conditions such as tuberculosis, rheumatoid arthritis, ankylosing spondylitis, and other spondylitic syndromes were excluded. The only consistent findings were those of osteoarthrosis—of the hands in five patients, the spine in four, and the knees in five. The signs of degenerative isease in the sternoclavicular joints were never severe, or did the joint changes justify a diagnosis of generalised steoarthrosis The significance of concurrent degenerative joint changes in these eight patients is doubtful, ince they were mostly asymptomatic and scrutiny of a omparable group of patients would certainly reveal ppreciable evidence of osteoarthrosis Nevertheless the veight of pathological evidence suggests that local degenrative changes in the sternoclavicular joints of people ver 40 is of ætiological significance In patients so redisposed, strain or unaccustomed use of the joint may rovoke acute arthritis

Once established, the arthritic signs and symptoms remain active, and the condition runs a chronic course In our series the symptoms persisted for 2–12 weeks (average 7 weeks) before the patients were referred to hospital. Rest and avoidance of the provocative factors did not give relief, but all the patients gained striking and lasting benefit from the intracapsular injection of hydrocortisone acetate 25 to 50 mg When further trauma provoked relapse, injection again proved effective

Summary

Nine patients, all over 45, presented with acute sternoclavicular arthritis One woman had chronic syphilis, and the arthritic signs receded with appropriate therapy The other eight (six women and two men) had degenerative changes in the sternoclavicular joints and a history of trauma or strain involving the affected joint

Degenerative changes are common in the sternoclavicular joints of people over 40, and acute arthritis with synovitis and capsulitis may be provoked by unaccustomed physical strain The condition tends to become chronic, but intracapsular injection of hydrocortisone speedily proved effective in all cases

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NICOTINIC ACID IN THE TREATMENT OF ISCHÆMIC HEART-DISEASE

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In ischæmic heart-disease the levels of β-lipoproteins and cholesterol in the plasma are usually above normal. Many investigators have shown that these raised levels can be lowered by large doses of nicotinic acid (Altschul et al 1955, Altschul 1956, 1958, Parsons et al 1956, Parsons and Flinn 1957, Achor et al 1958, Comesana et al. 1958)

Since 1946 I have been using nicotinic acid (combined with nicotinamide) in cases of acute myocardial infarction, angina of effort, and intermittent claudication This paper refers mainly to 36 patients with angina and 24 with myocardial infarction, seen in a practice of 2900 people After treatment with these vitamins attacks of anginal pain have steadily diminished, and in the large majority of cases have ceased entirely In myocardial infarction, injection of nicotinic acid has usually been followed by dramatic relief of pain and anguish

Nicotinic acid is a powerful vasodilator and has been used by a number of workers in the treatment of angina of effort Side-effects such as flushing, vertigo, and even collapse, have caused many to dislike it, and results have varied

Neuwahl (1942) gave a 0 5% intravenous infusion as a drip, having found the results of oral administration " uncertain " Brock (1942) reported that the immediate effect of giving nicotinic acid was " to relax spasm " Rook (1944) had good results in 14 out of 15 angina cases with intravenous nicotinamide. Moncrieff (1942), giving nicotinic acid by mouth in small doses, described its influence as " gratifying though irregular " From a controlled clinical trial in ten cases, however, Stokes (1944) regarded nicotinic acid as inferior to nitroglycerin as a vasodilator After this it was rarely used in ischæmic heart-disease. Aleksandrow and Kodejsko (1949) recorded benefit in 10 out of 15 cases treated with daily infusions of nicotinamide.

All these results were based on small series of cases

In 1946 I was searching for a vasodilator to replace nitroglycerin, which I found unsatisfactory (1) because it tended to induce headache (2) because its efficacy seemed to diminish with repeated use, and (3) because it did not seem to reduce the number of anginal attacks Unaware of the above observations, I gave 50 mg of nicotinic acid, by hypodermic injection, to a patient with acute myocardial infarction The effect was surprising in that the pain was relieved in fifteen minutes

Largely by trial and error, I developed a technique in which acute infarction was treated by both parenteral and oral administration of nicotinic acid and nicotinamide, and angina of effort with tablets

Treatment and its Results

Patients with a coronary thrombosis were given nicotinic acid 50 mg hypodermically and 100 mg under the tongue In 18 out of 25 patients a response was obtained after the first injection, but in 16 of these further injections were needed to maintain relief The response consisted in flushing of the skin, especially about the head and shoulders, this came on five to ten minutes after the injection and lasted for up to twenty minutes Usually the face was most affected, the lips and cheeks becoming suffused As the flush developed, the pain and shock subsided. Thus the shock might pass off very quickly, and it was striking to see a man who was grey and shocked become quite pink ten minutes after the injection The pain might recur as the flush passed off If it was severe, the injection was repeated, if it was moderate, 50 mg nicotinic acid was given by the mouth, being repeated hourly as necessary If no flushing occurred after the initial injection, two further injections were given at intervals of fifteen minutes If there was still no reaction, heparin 15,000 units was given, and the patient sent to hospital, but this was necessary in only 2 cases in the present series Morphine was avoided, because it was regarded as dangerous in coronary thrombosis The injection of nicotinic acid was usually followed by its administration by mouth, 100 mg thrice daily after food

In angina of effort, nicotinic acid was given after food, for, with the doses employed (up to 200 mg thrice daily), excessive vasodilatation was not uncommon, and this was minimised by administration on a full stomach Both in angina and in acute infarction, it was found that if half the dose was given in the form of nicotinamide a smoother and more sustained vasodilatation was obtained The nicotinamide was given before food, because its vasodilator effect was thought to be considerably less than that of the acid The dosage varied between 50 mg and 200 mg of each thrice daily (i e , up to 1 2 g of the combined vitamins daily) The usual maintenance dose was 150 mg of each, but if necessary the dose could be doubled, tripled, or even quadrupled

When vasodilatation was excessive, a condition like prickly heat occasionally developed, with pyrexia, itching, and considerable discomfort Warning of this possibility was always given to the patient He was told that the purpose of the treatment was to dilate the blood-vessels, that if this was achieved his face would flush, and that this was a desirable, expected, and harmless reaction Only 3 patients had excessive vasodilatation, and to these nicotinic acid had to be given in graduated dosage One patient fainted at the beginning of treatment the usual flushing was followed by a rebound effect of pallor and syncope Thus the treatment is not entirely without danger, and perhaps requires some experience When this patient's dosage was reduced to 50 mg (from 100 mg), all was well, and subsequently 100 mg thrice daily was taken without incident Occasionally, if the patient reacted badly to nicotinic acid, nicotinamide only was used, in graduated dosage, and it was always well tolerated One patient was hypersensitive to nicotinic acid, and went scarlet like a lobster, even to her eyeballs She too was successfully put on nicotinamide

As supplements, I usually gave other vitamins of the B group, and also ferrous gluconate

After two or three years' continuous treatment many patients who had been unable to walk more than a dozen paces without severe angina had no further attacks, and some were able to resume fairly heavy manual work such as that of milk roundsman or bus-driver Although this degree of improvement was more often seen in the 30–50 age-group, capacity for work often increased even in older people One woman, aged 75, was an invalid when treatment of her severe angina was started in 1950, now, at 84, she is active and keeps house for her son An outstanding effect of the treatment is the removal of the fear of impending death so common in angina, and also the fear of subsequent attacks

In coronary infarction not all results, of course, have been good 6 patients died, 4 from apparent massive thrombosis unresponsive to nicotinic acid 2 others (one a man of 59, the other a woman of 82) seemed to get considerable relief from the injections but died suddenly

4 of the angina patients also had intermittent claudication, and this was helped considerably by the nicotinic acid This was therefore tried in peripheral vascular disorders, especially Buerger's disease 3 patients with severe claudication and arterial obstruction demonstrated by arteriography recovered enough to resume their normal occupations

2 patients with classical pulmonary embolism were treated with large doses of nicotinamide and antibiotics They seemed to respond very satisfactorily

Diagnosis

Diagnosis both of angina and of coronary infarction was made on the history and clinical examination As only 2 cases of coronary infarction were sent immediately to hospital, the electrocardiograms were usually obtained later—sometimes much later Of the 25 cases diagnosed as infarction, 16 had electrocardiograms taken and all showed patterns indicating infarction Of the 40 patients with angina, abnormal electrocardiograms were found in 12, but a normal electrocardiogram was not held to invalidate the diagnosis A history of substernal pain on effort, radiating into the jaws or down the left arm, or a variation of this pattern of pain, was accepted, provided the pain was always induced by effort A standard exercise-tolerance test was used to evoke the pain during examination

Illustrative Cases

Coronary Thrombosis

Case 1—A man of 43, an insurance agent, had had increasing pain on effort since leaving the Army in 1946 On Oct 10, 1947, he collapsed with substernal pain He was pale and shocked when put to bed and given 50 mg nicotinic acid hypodermically Within ten minutes he became red in the face, and the pain subsided The effect of this injection and the next one lasted about two hours, after which the pain returned, and was so severe that he lay supine and immobile, in fear of imminent death He was given further injections and 100 mg. nicotinic acid every three hours by mouth After a week the pain subsided, in eight weeks he was ambulant, and he resumed work three months later Angina was still evoked by moderate exercise, but always relieved by nicotinic acid and nicotinamide taken by the mouth, which treatment was maintained for two and a half years, latterly intermittently

On Jan 3, 1951, about ten months after ceasing treatment, he had another infarction, for which he was given injections of nicotinic acid This attack was much milder, and against orders he got out of bed on the seventh day, when he developed a further infarction Recovery was fairly rapid with intensive treatment (three injections daily, with 150 mg of both amide and acid thrice daily by mouth) During convalescence, he was put on oral nitroglycerin for a fortnight, but he insisted on having the nicotinic-acid treatment, which he said was far superior

The angina has improved greatly It is still evocable by excessive effort, but he won a prize as the champion agent for his firm in the West Riding, and he remains active and well, maintaining treatment to this day With the angina he has had intermittent claudication, which is also controlled by the treatment

Case 2—A long-distance bus-driver, then aged 45, collapsed at the wheel July, 1949 After a night at hospital he was sent home When seen, he could not move without substernal pain, and his face was pallid, blood-pressure 150/95 mm. Hg He was given 150 mg nicotinic acid and nicotinamide by mouth thrice daily, and within a week his substernal pain and fear of something about to happen had disappeared He was ambulant after a week, and after a further month he returned to his work of tours bus-driver Treatment was maintained for two years quite regularly, and his angina ceased, but he disliked the discipline of constant regular treatment, and finally abandoned it

Gradually the angina returned, and in 1954 he had a severe attack of coronary thrombosis This time it occurred at night, and I was sent for He was ashen, immobile, and afraid to move, he spoke in a whisper and thought he was about to die He was given successive injections of 50 mg of nicotinic acid, with oral treatment of both acid and amide 100 mg each thrice daily After a rapid recovery, treatment was maintained for three years and his angina again disappeared Treatment then ceased. In 1957 his angina again returned fairly severely, and he came for further treatment This time an electrocardiogram was taken before treatment, and it showed a grossly abnormal pattern the cardiologist commented that it was very unusual for a patient with so abnormal a pattern to be so well nine years after the original and obviously severe infarction. Having rapidly responded to treatment, he maintains it conscientiously and has been well since. He continues his bus-driving.

Case 3.—A man now aged 62, a bus-driver, had a history of thyrotoxicosis ten years before, in 1946. In 1950, having gradually developed angina of effort, he was put on nitroglycerin tablets for a month without any benefit. He had an irregular pulse, 110 per min., and complained of substernal pain on effort, radiating into the jaws and down the left arm, blood-pressure 190/100. On nicotinic acid and nicotinamide he improved steadily, his anginal attacks going down from four a day to about twice a week, his range of effort became normal. After twelve months he became careless with his treatment, thinking that he was cured, but he maintained it intermittently for about three years.

Called to see him on Dec. 19, 1955, I found him grey, with acute air-hunger, a blood-pressure of 90/60, and a feeling of tightness in his chest, though without pain. Coronary thrombosis was diagnosed, and he was given two successive injections of nicotinic acid 50 mg. which relieved him considerably, and he was put on 450 mg. each of acid and amide which relieved him considerably. He was in bed for two weeks, and later an electrocardiogram demonstrated "unequivocal infarction." A cardiologist said that he would never work again as a bus-driver, but after three months he resumed his occupation and he has been driving continuously since. He is always careful to maintain treatment.

Case 4.—This lady was first seen in 1953, when she was 68 years of age and had typical angina of effort—severe enough to make her think of impending death. After three months' treatment with nicotinic acid and nicotinamide she was able to resume her duties as a magistrate, but she then became careless and ceased treatment. Early in 1954 she had a coronary thrombosis with shock, collapse, a drop in blood-pressure, and pain. She was given one injection only of nicotinic acid, followed by oral treatment with acid and amide, and also pyridoxine (300 mg. daily of each). She has carefully maintained treatment since then and keeps very well. She also had intermittent claudication of the left leg which began before the infarction, but which cleared up completely. It recurred when treatment was neglected.

Case 5.—At 66 years of age, this patient collapsed with a coronary thrombosis within the precincts of a hospital. She was kept in bed a month, and was treated with anticoagulants very successfully, but when she came home she still had angina when lying down, with angor animi. For a month she was kept on the hospital-recommended treatment of 'Mycardol' when this was changed to nicotinic acid and nicotinamide the difference was apparent. Her dyspnœa diminished and her angor animi disappeared very rapidly. In twelve months she was able to do a full housekeeping job. She has intermittent claudication of the left leg, which has not cleared up completely but does not prevent her from earning her living.

Angina of Effort

Case 6.—In 1950 this patient, then aged 50, had a blood-pressure of 230/120, an apex-beat in the anterior axillary line, and irregular rhythm with filling of the neck veins, gross albuminuria, gross dyspnœa of effort, and typical attacks of angina brought on by the slightest exertion. She was put on nicotinic acid and amide, 100 mg. of each thrice daily, with extra nicotinic acid for attacks of severe pain. She was also given digoxin 0.5 mg. daily, vitamin B_1 10 mg., and pyridoxine 10 mg., thrice daily. Her blood-pressure is now 170/100, her dyspnœa is very slight, and she gets no pain at all. Eight years ago she could not walk a dozen yards without acute dyspnœa, yet she manages a successful grocery shop.

Case 8.—A cinema attendant with labouring duties developed tightness of the chest and pain on effort and he consulted me six months later, in April, 1957. He was 52 years of age. After electrocardiography a cardiologist reported that he had ischæmic disease, and advised nitroglycerin. After three weeks of this his attacks of pain were fewer, but its severity was undiminished and he had headache almost every time he took enough nitroglycerin to relieve his pain. He was then put on nicotinic acid and amide 100 mg. each, thrice daily. His pain steadily diminished, and eventually disappeared. His electrocardiogram has reverted to normal.

Discussion

The response to nicotinic acid seems to depend on the stage of the infarction. When thrombosis is well established, little can be hoped from nicotinic acid or any other vasodilator. Thus in cases of massive thrombosis, and also perhaps in the elderly, anticoagulants remain the best means of treatment.

I have been impressed by the way in which the tendency to thrombosis has varied: in the younger patients spasm seemed to predominate. It is well known that in a proportion of cases no thrombosis can be demonstrated after a fatal infarction.

The fact that nicotinic acid is known to lower plasma-cholesterol levels (as was also seen in those of my cases where the cholesterol content of the blood was estimated) suggests that, unlike the nitrites, it does not act solely as a vasodilator. Though the doses found effective are far larger than those sufficient for relieving the kind of deficiency which causes pellagra, I believe that the concept of ischæmic heart-disease as a deficiency disease is worth pursuing. But my purpose here is simply to draw attention to the clinical efficacy of nicotinic acid as apparent in the cases treated in my practice during the past fourteen years. If the administration of nicotinic acid could give protection against the rising incidence of angina of effort and of coronary thrombosis, its more general use could be important.

Summary

Since 1946, 60 cases of ischæmic heart-disease (24 of infarction and 36 of angina of effort) have been treated with large doses of nicotinic acid and nicotinamide.

Injection of these remedies often give rapid relief in cases of myocardial infarction (especially where arterial spasm is a more important element than thrombosis), and on maintenance treatment with smaller doses by mouth many patients with angina have ceased to have attacks.

Given in large doses, nicotinic acid is a potent vasodilator, which must be used with caution. The fact that it lowers plasma-cholesterol levels suggests, however, that the benefit observed in cases of ischæmic heart-disease cannot be entirely ascribed to vasodilatation.

My thanks are due to Prof. R. E. Tunbridge for comments on an earlier draft of this paper. I am also grateful to Dr. H. T. Levi for repeated advice, encouragement, and criticism, and to Mrs. Abbishaw for her secretarial help.

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CHROMOSOME TRANSLOCATION AS A CAUSE OF FAMILIAL MONGOLISM

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EARLIER this year Polani et al (1960), examining the chromosomes of three mongols born to young mothers, found that one of these mongols had 46, not 47 chromosomes There were two chromosomes of pair 21, but one member of pair 14 (Standard System) was of unusual length and morphology They postulated that this abnormal chromosome had arisen by means of a translocation between a chromosome 14 and a chromosome 21, and noted that this would provide a mechanism for familial mongolism. Subsequent examination of peripheral blood has shown (J L H) that, in fact, the parents had a normal chromosome complement, therefore the translocation and non-disjunction in this patient must have occurred during gametogenesis in one of the parents or, less likely, in the embryogenesis of the child.

A large number of families of mongol patients attending The Hospital for Sick Children have been followed for up to ten years, and one of these families was felt to be the most suitable for testing the hypothesis that translocation might provide a mechanism by which some apparently normal parents are predisposed to have mongol children.

Investigation

The Family

A pedigree of this family is shown in fig. 1

The index patient M A (III 2 in the pedigree) attended The Hospital for Sick Children in 1952 at the age of one year and the diagnosis of mongolism was confirmed. In addition to the usual facial stigmata (see fig 2), his palm prints were characteristic of mongolism [summed a t d angles at the age of 9 years are 166°, the mean in normal children being 88°±16° (Penrose 1954)]

This boy is an imbecile who now attends an occupation centre He has no other congenital malformations In November 1953, M A 's mother (II 6) had another boy (III 3) who died of congenital heart disease at the age of 5 months He, too, was a mongol. The third boy (III 4), born in October, 1958, is normal. In September, 1958, M A 's maternal aunt (II 3) had her first and only child, a boy (III 1) who died at the age of 5 hours, probably of birth injury, and was also noted to be a mongol Neither M A 's mother nor his aunt have had any miscarriages Both these women and their mother (I 1) were of at least average intelligence and fitness

CHROMOSOME-COUNTS IN THE INDEX PATIENT (M A) AND HIS RELATIVES

—	Diploid number	Chromosome-counts				Total cells	No of cells analysed
		< 15	15	46	47		
M A (III 2)	16†	3*	—	25	2*	30	(6)
Mother (II 6)	15†	9*	27	3*	—	39	(6)
Mother's mother (I 1)	15†	3*	8	—	—	11	(2)
Mother's sister (II 3)	15†	8*	7	—	—	15	(3)
Father .	16	—	—	15	—	15	(3)
Brother	16	17*	6*	20	—	43	(6)

† Translocation present * Cells broken

M A. had two maternal uncles (II 1 and 2) and two further maternal aunts (II 4 and 5), all of whom had died in infancy of bronchitis or bronchopneumonia The death certificates of these children do not mention mongolism, but this does not exclude the possibility that one or more of them were mongols

The Findings

The chromosome analyses were made from short-term cultures of peripheral blood by a modification of the technique of Hungerford et al (1959) The Standard System (Denver) of nomenclature (*Lancet* 1960) was used

The chromosomes of M A, his surviving brother, his mother, father, maternal aunt, and maternal grandmother were examined. The counts are summarised in the table

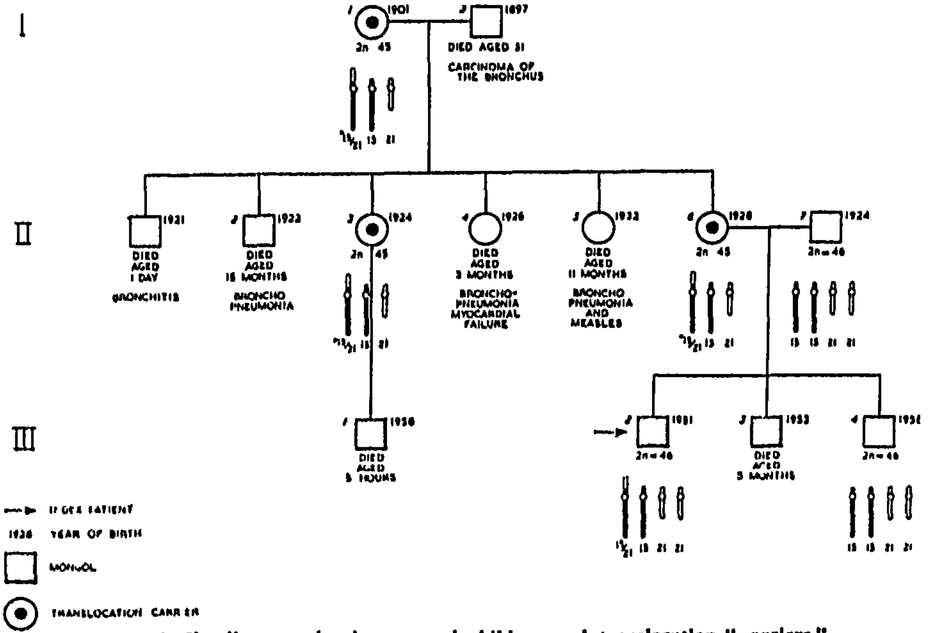

Fig 1—Family tree showing mongol children and translocation "carriers"

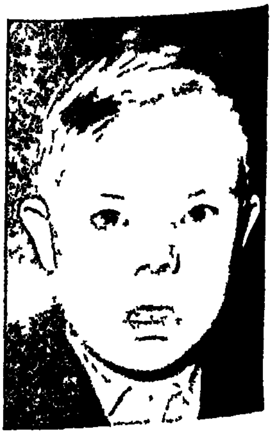

Fig 2—The index patient

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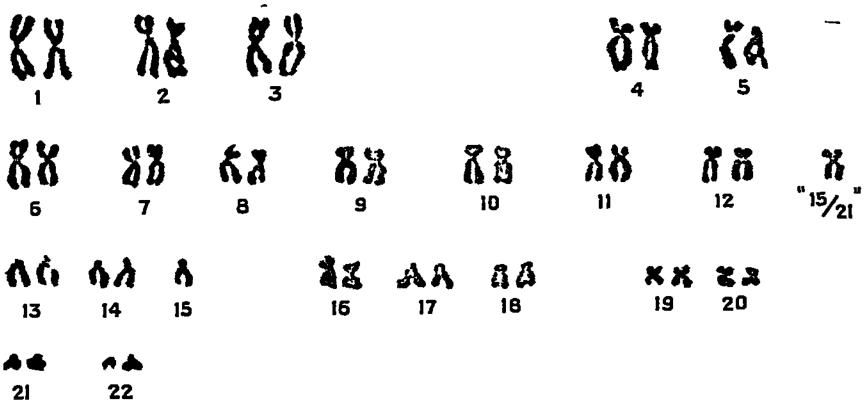

Fig 3—Analysis of the karyotype of the index patient (III.2)—Standard System

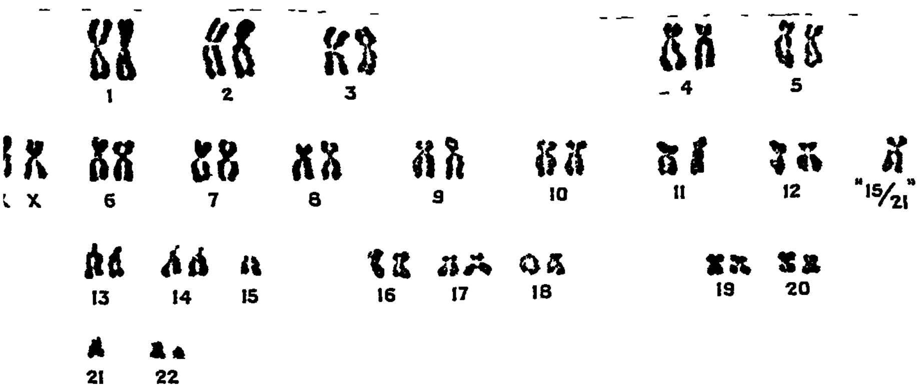

Fig 4—Analysis of the karyotype of the mother (II.6)—Standard System.

M.A's count was 46. Those of his mother, maternal aunt, and maternal grandmother were all 45. His father's (II 7) and brother's counts were 46, with normal chromosomes. M.A.'s karyotype is shown in fig 3.

This shows only 4 chromosomes in the 21–22 group plus one Y chromosome, as in a normal male, whilst in the 13–15 group 5 instead of 6 chromosomes were observed. In group 6–12, an additional submetacentric chromosome was seen.

The karyotype in M.A.'s mother (fig 4) was identical with that of her sister and her mother.

This shows only 3 chromosomes instead of 4 in the 21–22 group, 5 instead of 6 in the 13–15, and an additional chromosome in the group 6–12 similar to that seen in M.A.

The 6–12 groups of the four individuals are shown together in fig 5, and the similarity of the additional chromosome in this group in each individual may be seen.

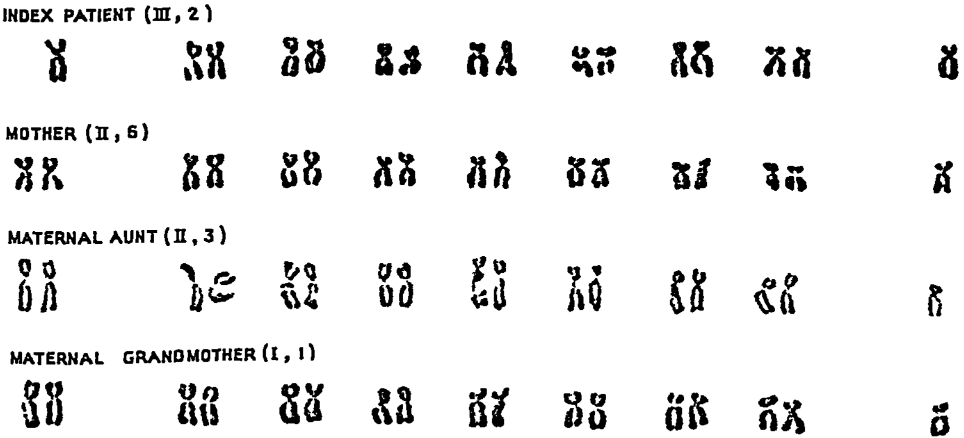

Fig 5—Comparison of the 6-12 groups in the four members of the family carrying the translocation.

Interpretation

Because mongolism appears to require the presence in triplicate of the genetic material of chromosome 21, it is logical to assume that this is also the case in patient M.A. We therefore consider that the additional chromosome in the 6–12 group in all four individuals has arisen by means of a translocation, probably between chromosomes 21 and 15, at least as early as gametogenesis in the maternal grandmother's parents, or the embryogenesis of this grandmother. Examination of the additional chromosomes suggests that it is the same chromosome being inherited throughout the family.

The suggested mechanism for the translocation and its inheritance is shown in fig 6.

It is, however, by no means certain that the four possible types of gamete will occur with equal frequency. This will be greatly influenced by the pairing behaviour of the translocation at meiosis.

Discussion

The clinical interest of the finding of "carriers" of a translocation, which may cause mongolism, is that it may make it possible both to be more precise in advising parents on the risks of their having a second mongol child, and to detect relatives of mongols who themselves have high risks of having mongol children. Experience at The Hospital for Sick Children has shown that the risk of parents having a second mongol child is almost certainly raised above the random risk, especially at the younger maternal ages. It has not, however, been possible to show whether this is in most part an overall increase, or whether there are two groups of mongols, a majority with little, if any, increase in the risk of recurrence, and a minority with a relatively high risk. It is now important to discover, by systematic study, the extent to which the rare occasions in which one or other parent has an abnormal karyotype may account for the overall increased risk of recurrence of mongolism.

It is, perhaps, surprising that the "carriers" of the

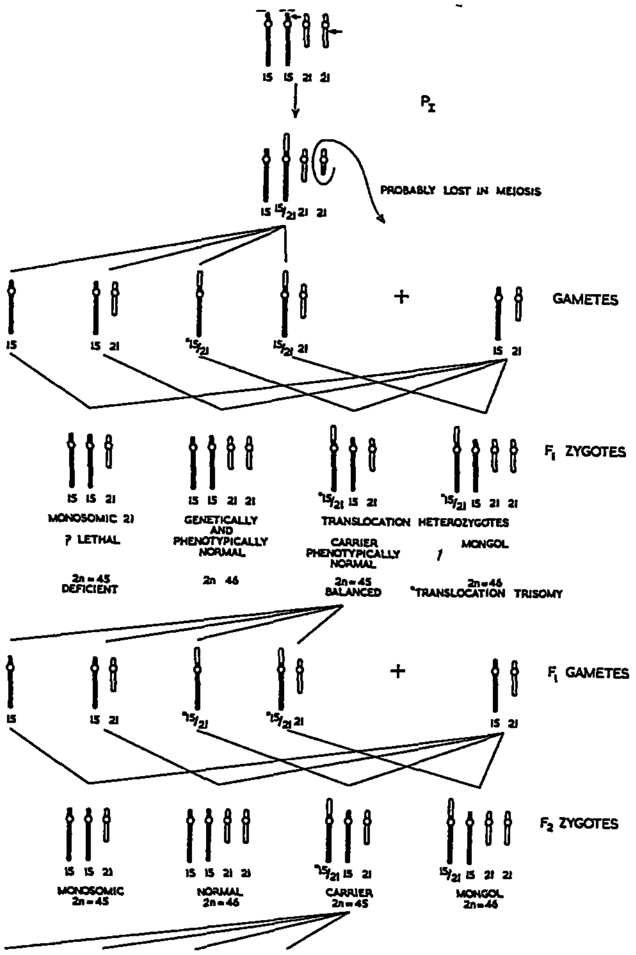

Fig 6—Diagram to show the origin of the suggested translocation and its mode of inheritance

translocation are apparently normal They have, however, presumably lost very little chromosome material, only part of the two short arms of chromosomes 15 and 21

There are two other instances in which the parent of a mongol child has been found to have an abnormal karyotype In the first family (Fraccaro et al 1960) the father is reported to have had 47 chromosomes, it is difficult to interpret the situation in this family In the other family the situation appears from the preliminary communication (Penrose et al 1960) to be very similar to that in the present family

It is noteworthy that all the examples of presumed chromosome translocation that have been reported in man involve the acrocentric chromosomes, which tend to lie close together at interphase in association with the nucleolus (Polani et al 1960)

Summary

A family is described in which a translocation, probably between chromosomes 15 and 21, occurring at least as early as the embryogenesis of the grandmother, was responsible for mongolism in three of her grandchildren and possibly one or more of her children Further studies are needed to see what proportion of the overall increased risk of recurrence of mongolism in later siblings is due to such recognisably abnormal karyotypes in a small minority of the parents of mongol children

We should like to thank the members of the staff of The Hospital for Sick Children for access to their patients, Dr J A Fraser Roberts for advice and encouragement, and Miss V M McGuire, Miss A Horsley, and Mr S L Yapp for their skilled technical assistance

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RENAL MEDULLARY NECROSIS FOLLOWING EXSANGUINATION IN INFANCY

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Necrosis of the renal papillæ is diagnosed usually post mortem, but occasionally during life (Robbins and Angrist 1949, Swartz 1954, Cates and Hewer 1956) Many of the reported cases have been in diabetics with acute pyelonephritis, in non-diabetics the condition is usually associated with urinary obstruction and superimposed infection Recently phenacetin consumption has been associated with papillary necrosis as part of a true chronic interstitial nephritis (*British Medical Journal* 1960)

Papillary necrosis in infancy without pyelonephritis or urinary obstruction has rarely been reported One of the cases described by Swartz (1954) was a 5-month-old infant with *Pseudomonas aeruginosa* meningitis, cerebral atrophy, and bilateral papillary necrosis This disorder was also noted by Morison (1945) in renal-vein thrombosis in the newborn

The following case does not resemble the hitherto published cases of renal papillary necrosis in adults, except case 7 of Swartz and Hoogstraten (1959), where, in a woman, shock incidental to trauma to the right kidney led to bilateral papillary necrosis The lesion is similar in distribution to that in the infant described by Swartz (1954)

Case-report

The infant, a Bantu female, was born on the morning of Aug 14, 1959, no details were available At 5 P M that day the infant was brought to a maternity home, pulseless and exsanguinated, having bled from the umbilical cord A rapid transfusion was given of 180 ml of group-O rhesus-negative blood, not cross-matched as the infant was moribund. The infant responded well 2 5 mg of 'Synkavit' (a vitamin-K analogue) was given intramuscularly That night the infant bled from the mouth and vagina, and was given a further 5 mg of synkavit intramuscularly After being quite well for the following two days, the infant suddenly died

Necropsy

Postmortem examination was carried out four days after death (the body was refrigerated) Weight 2914 g , length 49 cm The body was that of a full-term infant

Lungs (right 20 g , left 17 g) showed subpleural hæmorrhages and congestion *Kidneys* (20 g) showed no special external features The capsules stripped easily On section all the renal pyramids and inner portions of the medulla were strikingly pale yellow-white, contrasting vividly with gross congestion at the corticomedullary junctions (fig 1) The cortex was paler pink than usual The medulla of both kidneys was diffusely, uniformly affected No thrombosis was evident in the inferior vena cava, the main renal veins at the hila, or their branches, but the junctions of the main renal veins with the inferior vena cava were not dissected *Stomach* showed

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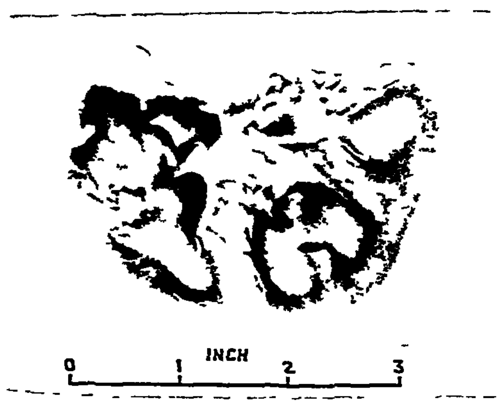

Fig. 1—Section through kidney, showing diffuse nature of the process with hyperæmia and hæmorrhage at corticomedullary junction and pallor of medulla.

notable changes Mainly in the body and lesser curvature were numerous submucosal hæmorrhagic nodules up to 0 5 cm. in diameter, often confluent, and covered with yellow-grey exudate. Intervening mucosa was œdematous Smear showed numerous gram-positive bacilli. *Large intestine* contained three similar areas *Small intestine* was normal. The other organs showed no abnormal features

Microscopic Findings

Kidneys showed complete coagulative necrosis of the entire inner medulla and papillæ, involving the collecting tubules and some loops of Henle (fig 2) The outlines of the tubules were well preserved, the tubules being filled with dead cells, many having faded nuclei. There was slight patchy cellular reaction of histiocytes and polymorphs In the medulla adjacent to the necrotic area was a zone of hæmorrhage, merging with a zone of intense hyperæmia with dilated capillaries, and viable loops of Henle and collecting tubules Some glomeruli were filled with blood, others were bloodless, but all were intact. Near the boundary zone some proximal and distal tubules of the cortex were necrotic in an irregular, patchy fashion. The bulk of the cortex, however, showed no abnormal features The process was identical in both kidneys No organisms were revealed by Gram's stain. Section through the renal hila showed normal veins and arteries with no thrombosis *Lungs* showed congestion and intraatrial hæmorrhages Some atria contained a faint hyaline membrane. *Stomach* contained numerous submucosal and mucosal hæmorrhages Thrombosed submucosal veins were present. Mucosa above this was necrotic (or autolysed), and covered by exudate containing fibrin and scanty degenerate polymorphs, gram-positive bacilli, and gram-positive cocci. *Colon* was similar to stomach. *Uterus* showed hæmorrhagic endometrium with no glandular structures Sections of other organs showed no special features

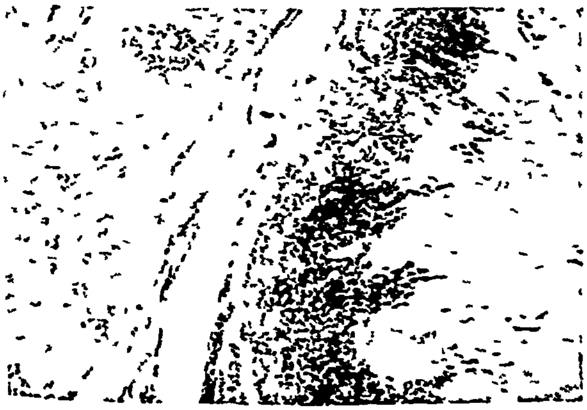

Fig 2—Low-power view of section from kidney, showing, from left to right, relatively intact cortex, arcuate artery, zone of hyperæmia and hæmorrhage, and necrosed medulla.

Discussion

Renal Findings

The most striking feature in this case was the renal lesion. The medullary and partial tubular necrosis was of very recent origin. No signs of infection were present The bilateral uniform distribution pointed strongly to a vascular change

In the infant described by Swartz (1954) the distribution of the renal changes was similar, but thrombi were prominent in the intrarenal veins In renal vein thrombosis there was usually gross congestion and hæmorrhage affecting most of the renal medulla and some of the cortex. In the present case, though the entire lengths of the renal veins were not dissected out towards the inferior vena cava, the vessels at the hila were not thrombosed, nor were the intrarenal veins thrombosed microscopically, and the inferior vena cava was normal. This case is therefore rather different from that of Swartz and those of Morison (1945)

The profound hypotension soon after birth may have been crucial in the pathogenesis of the renal lesion. Persistent renal vasospasm after hypotension is well known. On this basis lengthy oligæmic shock has often been followed by acute tubular necrosis, but medullary necrosis has not been attributed to this mechanism In case 7 of Swartz and Hoogstraten (1959) shock with consequent vascular stasis in the renal medulla was suggested as a causal factor The papillæ have a poor blood-supply compared to the rest of the kidney, but are less active functionally, which may partly explain why papillary necrosis has not been reported in these states In the majority of reported cases, only with infection and/or renal obstruction has papillary necrosis developed. In the present case proximal tubules were necrosed, but the medulla was mainly affected. If the usually accepted type of hypotensive vasospasm is operative in neonates, why was the ensuing lesion here so paradoxical? It is also an interesting reverse of the cortical necrosis of the kidneys found sometimes in concealed accidental intrauterine hæmorrhage Vasospasm may possibly have differed from the usual pattern by involving medullary rather than cortical arteries and arterioles

Similarity to Experimental Lesions

Experimentally renal medullary necrosis has been produced in animals by the injection of tetrahydroquinoleine (Rehns 1901), vinylamine (Levaditi 1901, Mandel and Popper 1951), bromethylaminbromhydrate (Oka 1913), and mono-*N*-methyl-alanine (White and Mori-Chavez 1952) In the rabbits injected with vinylamine by Mandel and Popper (1951) ischæmic medullary necrosis developed, attributed to tissue anoxia caused by excessive medullary hyperæmia, vasoparalysis, and multiple thrombus formation In the present case the lesions closely resemble the lesions of these rabbits in the early stages, except for the absence of thrombosis Thrombosis in the rabbits might have been a secondary feature, stasis being the primary damaging factor—which would suggest that in both instances a similar vascular response occurred to different stimuli

In rabbits Sheehan and Davis (1959), after applying a complete pedicle clamp to the kidney, found that the incidence of failed reflow through the medulla was directly related to the duration of the initial ischæmia, reflow never occurring after clamping more than two hours This failure was unrelated to death of the tubules Medullary tubules could survive a two-hour period of ischæmia, and, if circulation was re-established at that time, most remained alive Sheehan and Davis concluded that, when the medulla had become infarcted, it had been alive at the end of the period of pedicle-clamping and that it died subsequently because circulation was not re-established through it, for reasons unknown In the present case, though no glomerular changes were noted, the similar renal findings support an ischæmic origin

The possibility remains of a toxic cause of the renal lesion, perhaps operating through a vascular mechanism The only drug known to have been given to the infant—synkavit—is not known to result in this lesion The clinical and pathological course was not that seen in massive hæmolysis after blood-transfusion Lastly, a gastrointestinal infection (see below) may have caused septicæmia or toxæmia, or both, acting selectively mainly on the renal medulla The features here do not confirm this, but notoriously neonatal septicæmia can be undiagnosable except bacteriologically

Bleeding from Multiple Sites

The initial hæmorrhage in this infant was from the umbilical cord, no cause for which was apparent Blood-transfusion was followed by bleeding from the mouth and vagina The vaginal bleeding probably followed endometrial changes due to œstrogen withdrawal after birth The gastrointestinal and pulmonary hæmorrhage seen at necropsy may have been secondary to uræmia The blood-urea was not estimated, but, as the infant died two days after the initial catastrophe, and as, judging from the histological findings, practically no renal function was possible, some uræmia may reasonably be assumed Hæmorrhage from the gastrointestinal tract may occur in uræmia in children (Nelson 1954)

The gastrointestinal changes may have been infectious in origin, but unfortunately the exudate was not cultured, and only histological assessment has been possible, and this was difficult owing to severe necrosis or autolysis

Summary

In a case of bilateral renal medullary necrosis in a neonate, the lesion apparently differed from the papillary necrosis usually found in adults, but resembled lesions produced in rabbits by injection of vinylamine or by complete clamping of the renal pedicle Ischæmia following exsanguination is thought to underlie the lesion

My thanks are due to Prof J G Thomson and Dr C J Uys for their valuable advice, and to Dr M Berman for the photographs

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> " And, please recall that the so-called art of medicine is a supplement, not a substitute, for science "—WILLIAM ENGSTROM, *Marquette med Rev* 1957–58, 23, 3

EFFECT OF INTERFERON ON EXPERIMENTAL VACCINIA AND HERPES-SIMPLEX VIRUS INFECTIONS IN RABBITS' EYES *

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THE inhibiting effect of interferon (Isaacs and Lindenmann 1957) on the multiplication of various viruses in tissue cultures and in chick embryos has been clearly demonstrated (Henle et al 1959, Ho and Enders 1959, Isaacs 1959, Porterfield 1959, Wagner 1960) But the activity of interferon in vivo has so far been proved only by its ability to inhibit locally the development of vaccinia lesions in rabbit skin when injected before or along with the virus (Lindenmann et al 1957, Isaacs and Westwood 1959)

In this paper we describe the effect of interferon on the course of experimental vaccinia and herpes-simplex infections in the rabbit's eye

Material and Methods

Preparation of Interferon

Trypsinised rabbit-kidney cells were grown in Roux bottles in 70 ml of the following medium 40% Hanks' solution and 60% of a mixture containing equal amounts of the aminoacid constituent of Parker's solution, and pooled inactivated Seitz filtered human serum When uniform sheets of cells were obtained the medium was replaced with the following maintenance medium 50% Hanks' solution, 47 5% of the amino-acid constituent of Parker's solution, and 2 5% inactivated filtered calf-serum

The Enders strain of mumps virus was used for the production of interferon The dialysed virus allantoic fluid was inactivated by ultraviolet irradiation, using a similar method to that described by Henle and Paucker (1958) In our hands, irradiation for 45+45 sec made the virus non-infective for chick embryos

The cell-cultures were seeded with 35 ml of irradiated virus (1024 hæmagglutinating units per ml) and 35 ml of maintenance medium After 3 hours' incubation at +37°C the cultures were washed five times and refed with 70 ml of maintenance medium. The bottles were then further incubated for 24 hours at +37°C, and the medium was collected after vigorous shaking This was ultracentrifuged for 60 min (Spinco model L) at 34,906–73,300 *g* The supernatant served as interferon The interfering factor liberated by identical virus treatment of human cell-cultures matched the properties of interferon (Cantell 1960)

Control preparations were made in exactly the same way but using normal allantoic fluid instead of irradiated virus

Experiments on Rabbits' Eyes

The vaccinia virus used was the Finnish vaccinia strain In previous experiments we had found that a stock virus, containing at least $10^{7\,5}$ egg-infective doses per ml, was capable of causing an apparent infection in the rabbit's eye only when inoculated undiluted Therefore we again used an undiluted inoculum

We had some difficulty in finding a strain of herpes-simplex virus which was pathogenic to the rabbit's eye The first attempts, with two strains recently isolated in primary human amniotic cells from human keratitis, were completely unsuccessful Thereafter two other strains of herpes virus, also derived from human eyes, were combined, and with an undiluted inoculum of this combined strain a distinct infection was produced consistently in the rabbit

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* Aided by grants from the Sigrid Jusélius Foundation.

TABLE I—EFFECT OF INTERFERON ON EXPERIMENTAL VACCINIA-VIRUS INFECTION IN RABBITS' EYES

Day	Part of eye	Rabbit 1		Rabbit 2		Rabbit 3		Rabbit 4	
		Interferon	Control	Interferon	Control	Interferon	Control	Interferon	Control
5th	Lids	−	−	−	Ectropion	−	Ectropion	−	Ectropion
	Conjunctiva	−	−	−	+++	−	−++	=	+++
	Cornea	−	+	+	+++	+	+++	++	+++
	Uvea	−	−	−	−	−	±	−	−
7th	Lids	−	−	−	Ectropion	−	Ectropion	−	Ectropion
	Conjunctiva	−	−	−	−++	+	++−	+	+++
	Cornea	−	+	±	+++	+	+++	+	+++
	Uvea	−	−	−	+++	−	+	−	+++
9th	Lids	−	−	Ectropion	Ectropion	−	Ectropion	Ectropion	Ectropion
	Conjunctiva	−	−	++	+	−	++	++	+++
	Cornea	−	+(scar)	+−	+	+	+	+++	+
	Uvea	−	−	+−	++	+++	+++	+++	+++
14th	Lids	−	−	−	−	−	−	−	−
	Conjunctiva	−	−	−	−	−	−	−	−
	Cornea	−	+(scar)	++(scar)	++(scar)	−(scar)	++(scar)	+(scar)	++(scar)
	Uvea	−	−	−	−	−	−	−	−

− =no symptoms
± to +++ =increasing degrees of symptoms

Symptoms of infection were
Lids—ectropion.
Conjunctiva—congestion, chemosis, exudate.
Cornea—ulcers, scar
Uvea—congestion, œdema of iris, turbid aqueous humor

A superficial scarification was made on the cornea of anæsthetised white rabbits with a trepan, giving a circular lesion of 5 mm diameter 0 05 ml of virus was then instilled on the cornea Immediately after virus inoculation, about 0 2 ml of interferon was dropped into the right eye, and 0 2 ml of the control preparation into the left eye This application was repeated during the next 4 days, about six times daily The eyes were then inspected every 2nd day When lesions had developed, both macroscopic and biomicroscopic examinations were made Fluorescein staining facilitated the estimation of corneal lesions For brevity, the right eye will be termed below the interferon eye, and the left eye the control eye

Interferon alone was instilled as described above on the eyes of two rabbits in order to study the possible toxic effects of interferon

Results

No toxic effects could be found in the eyes treated with interferon alone

Table I shows that the onset of an apparent vaccinia infection was clearly delayed, in the eyes treated with interferon, for 4 days after virus inoculation Furthermore the disease was milder in the interferon eyes than in the control eyes In rabbit 1, in which the disease in the control eye was milder than in the other rabbits, the interferon eye remained completely free from infection The findings in table I also suggest that the superficial parts of the eye were better protected by interferon than the deeper parts Results similar to those given in table I were also obtained earlier in preliminary experiments with two rabbits

The herpes-simplex infection (table II) was more rapid and severe than the vaccinia infection The course of infection varied considerably in individual eyes, but no clear and consistent difference could be observed between interferon eyes and control eyes

Discussion

Our results confirm the finding of Isaacs and Westwood (1959) that interferon can inhibit virus growth in vivo without any obvious toxic effects Our test system would no doubt have been more sensitive to any toxic effects of interferon than that of Isaacs and Westwood, but biomicroscopical examination of interferon-treated eyes did not reveal any toxic changes in the eyes

The lack of effect of interferon in herpes-simplex infection of rabbits' eyes is in line with earlier findings on the resistance of the herpes virus to interferon on chick chorion (Isaacs et al 1958) and in tissue cultures (Ho and Enders 1959)

In the hands of Isaacs and Westwood (1959) interferon could "completely" protect the rabbit skin against vaccinia virus, when the dosage and timing were appropriately adjusted In view of the low concentration of interferon which we used, the application of interferon mainly after the virus, and the large dose of virus inoculum, it is not surprising that we obtained only partial protection of the rabbit's eye against vaccinia virus On the other hand, one cannot exclude the possibility that the delayed vaccinia infection in the interferon-treated eyes was due to reinfection from the untreated eye of the same rabbit rather than to incomplete effectiveness of interferon

Slight signs of infection are more easily observed in the eye than in the skin Attempts are now in progress to suppress vaccinia infection in rabbits' eyes by prolonged treatment with concentrated interferon preparations

If interferon can be used in man without harm, superficial viral infections of the eye might very well lend themselves to the study of the activity of interferon Some

TABLE II—EFFECT OF INTERFERON ON EXPERIMENTAL HERPES-SIMPLEX INFECTION IN RABBITS' EYES

Day	Part of eye	Rabbit 1		Rabbit 2		Rabbit 3		Rabbit 4		Rabbit 5	
		Interferon	Control	Interferon	Control	Interferon	Control	Interferon	Control	Interferon	Control
3rd	Conjunctiva	−	+	−+−	+	+	+	−	+	+	+
	Cornea	−	+	+++	++	−	++	++	++	+++	+++
	Uvea	−	±	−++	−	−	−+	+	+	+	+
5th	Conjunctiva	+	−++	+++	−−+	−	++	+++	+++	+++	++−
	Cornea	±	−++	+−+	±	±	++	+−+	+−+	+++	+++
	Uvea	−	−−+	−−+	−	+	−+	+−+	−−+	+++	+++
12th	Conjunctiva	−	−	Panophthalmitis	−	−	−	−	−	Panophthalmitis	Panophthalmitis
	Cornea	− (scar)	+− (scar)		−− (scar)	+ (scar)	++ (scar)	−++ (scar)	+− (scar)		
	Uvea	−	−		−	++	++	++	−−		

The symptoms, and their degree, were as shown in table I.

of these diseases still constitute an important and difficult medical problem

Summary

The external application of interferon (derived from rabbit-kidney cells) on the eyes of six rabbits for 4 days following corneal inoculation of vaccinia virus, clearly delayed and suppressed the symptoms of infection The same interferon treatment did not affect the course of herpes-simplex infection in the eyes of five rabbits

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A FATAL CASE OF ECZEMA VACCINATUM

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ECZEMA vaccinatum, a serious disease in which multiple vaccinial lesions arise on eczematous skin, is rare and should be largely preventable The following case is presented to draw attention to the continuing occurrence of the disease, although the danger of vaccinating members of eczematous families has been known for half a century (Dock 1906) (The classification of vaccinial complications suggested by Lewis and Johnson [1957] is followed)

Case-report

An unvaccinated girl, aged 2 years, of mixed European and West Indian descent, had had infantile eczema since she was 3 months old This affected the forehead, arms, and legs, and it had been treated with cremor zinci et ung picis carb 2%, and hydrocortisone cream 1% for exacerbations

4 days before the child's admission to hospital a vesicular eruption had appeared on the legs, and had spread to the arms and face 10 days before this her younger brother had been vaccinated He had a typical primary reaction on his upper arm, which was uncovered, and he also had slight eczematous lesions of his neck The parents said that when he was vaccinated no inquiry had been made about a family history of skin disorder The patient was not known to have been in contact with the herpes-simplex virus, and she had had no other illnesses

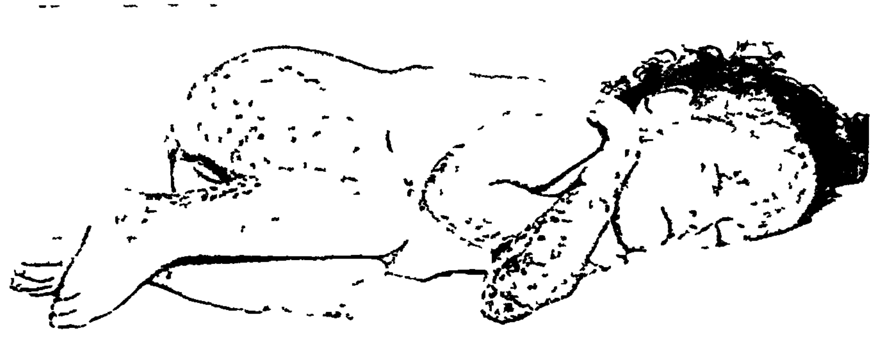

Fig 1—Skin lesions at the time of admission to hospital.

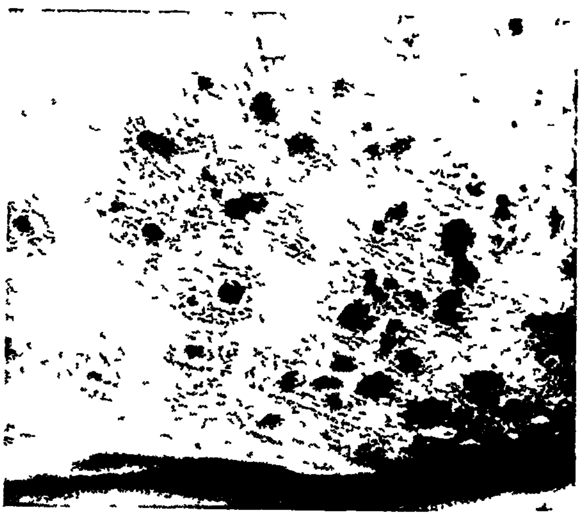

Fig 2—Part of the thigh, showing the umbilicated vesicular eruption

Physical Findings

On admission to hospital the child was ill and slightly dehydrated. Her temperature was 102 6°F, pulse-rate 110 per min , and respirations 30 per min A severe umbilicated vesicular eruption (fig 1), with lesions 5–10 mm. in diameter, affected the forehead, eyelids, cheeks, chin, arms (from just below the axillæ downwards but excluding the palms and fingers), and legs (from the groins downwards but sparing the toes and soles) There were a few isolated lesions on the buttocks and abdomen, but none were seen inside the mouth or on the conjunctivæ This distribution accurately followed that of her eczema The rash was confluent in many areas (fig 2), and exuded fluid which was mostly clear, though in some places it was bloodstained Irritation was intense, and there was secondary infection on the forehead Small discrete lymph-glands were palpable in both anterior triangles of the neck, but not elsewhere

A diagnosis of eczema vaccinatum was made

Course, Treatment, and Laboratory Findings

The child was nursed with sterile precautions, the affected areas being exposed The limbs were tied to a cradle to prevent scratching Sedatives, antibiotics, and fluids were given at first by mouth, and from the 6th day by intravenous infusion Antivaccinial gamma-globulin 1 g was given intramuscularly for 2 days following admission, 0 75 g was given on the 9th day, and 1 g on the 11th day Gamma-globulin and neomycin ($^{1}/_{2}$%) eyedrops were instilled daily into the conjunctivæ Chlortetracycline $^{1}/_{2}$% cream was applied to the skin

By the 4th day a few new lesions had appeared, and there was generalised lymphadenopathy and enlargement of the liver

On the 6th and 9th days the child had episodes of hypothermia to 89 4 and 87 0°F, each lasting several hours These responded to intravenous hydrocortisone and local heating

On the 9th day the hæmoglobin was 72% (Haldane), and the blood-urea 10 mg per 100 ml Plasma-proteins totalled 5 1 mg per 100 ml. (albumin 2 7 mg and globulin 2 4 mg) The cerebrospinal fluid was normal By this time the rash was mostly confluent and exuding large quantities of fluid, in many areas the full skin thickness was lost The child also had intermittent diarrhœa

On the 10th to 11th days there was a 24-hour period of anuria, during which the blood-urea rose

54 mg per 100 ml. Blood-cultures grew coagulase-positive aphylococci. The child died next day

ostmortem Findings

The skin was as described above. Large fleshy lymph-lands were found in the axillæ, the groins, and the neck. he brain was normal. The lungs were œdematous, with atches of early consolidation. Several freshly ulcerated areas ere seen in the stomach, the largest being 2 cm. in diameter nd covered with fresh sloughs There were small patches of nflammation in the postcricoid region of the œsophagus and t its lower end, but no ulceration of the small or large ntestine. The liver showed severe fatty changes, and the idneys were pale and slightly swollen. The spleen and drenals were normal.

ostmortem Virology and Bacteriology

The vaccinia virus, and resistant staphylococci and fæcal treptococci, were isolated from specimens of skin and organs aken post mortem.

Discussion

Probably the first record of generalised vaccinia (wide-spread vaccinial lesions on normal skin) is the case described by Conzals in 1810 (Tedder 1936) The patient contracted the disease after sniffing powdered vaccination scabs, cutaneous vaccination having failed. Hutchinson (1879) reported another which appeared after normal vaccination.

The first description of vaccinial lesions appearing on eczematous skin was in 1882 by Martin, who recorded the case of a child with atopic eczema on whose skin widespread vesicles had appeared after the mother and brother had been vaccinated 5 years later Kaposi (1887) described similar cases, and as a result the clinical syndrome in which umbilicated vesicles are superimposed on skin disease is known as Kaposi's varicelliform eruption If this eruption appears on atopic eczema and is caused by the herpes-simplex virus it is designated eczema herpeticum, or by the vaccinia virus, eczema vaccinatum (Tedder 1936) Clinically the two are indistinguishable (Lewis and Johnson 1957, Sexton et al 1957)

In 1906 Dock, reporting Blochmann's work, drew attention to the danger of vaccinating the members of eczematous families, and since then there have been many reports of widespread vaccinial lesions superimposed on atopic eczema (Graves and Dowman 1937, McKhann and Ross 1938, Strickler 1944, Hershey and Smith 1945, Fries et al. 1948, Fasal 1950, Kempe and Benenson 1955, Sexton et al 1957, Lewis and Johnson 1957, Reynolds and Joos 1958, &c)

The incidence of generalised vaccinia and eczema vaccinatum is uncertain, since many cases are probably not reported. Until recently the two diseases have not been clearly differentiated, and their combined incidence is probably between 1/50,000 and 1/100,000 vaccinations (Jubb 1943, Reynolds and Joos 1958) In Jubb's large series the case-mortality was 11 7%, or 1 2 deaths per million vaccinated.

The largest recorded series of eczema vaccinatum is that of Fries et al. (1948) who found an incidence of 1/150,000 in the mass vaccinations in New York in 1947 The case-mortality was 4% Case-mortalities up to 40% have previously been reported (Kempe and Benenson 1955)

Probably two-thirds of all cases of widespread vaccinia have skin disease—mainly atopic eczema (Hershey 1945) —and eczematous subjects run a very much higher risk of contracting cutaneous vaccinial lesions than do those unaffected by skin disorders (Fries et al 1948) Fries et al. observed sixteen cases of eczema vaccinatum, in one New York hospital, all of which had atopic eczema affecting the limbs, cheeks, and neck. Only one had been vaccinated (3 years previously), and all had been in contact with recently vaccinated people. 70% were under 2 years old

The disease is usually transmitted by direct contact between skin and virus (Lewis and Johnson 1957) But hæmatogenous spread localising to disordered skin is possible as was shown by Calmette and Guerin (1901), who found that laboratory animals injected intravenously with vesicular fluid developed vesicles on previously scarified skin.

In the absence of skin disease the lesions may be localised to areas of direct contact with the virus (secondary or satellite vaccinia) But, with hæmatogenous spread the typical distribution of the rash (which appears 7–11 days after contact with the virus in 80% of cases) is centripetal, the trunk being affected more than the limbs (Jubb 1943) In the presence of eczema and other skin diseases, however, the lesions are confined almost exclusively to the affected areas (Hershey and Smith 1945, Reynolds and Joos 1958)

Conclusions

In the case presented here the history of atopic eczema and of contact with a recently vaccinated sibling, the distribution and characteristics of the rash, and the course of the illness, are typical

The skin of candidates for vaccination should be examined carefully, and no-one with significant skin disorder should normally be vaccinated, though in a smallpox outbreak balanced assessment of the relative risks has to be made In doing this the area of diseased skin is important, the larger this area the more serious the eczema vaccinatum should it arise

Before vaccination a careful history should be taken for evidence of skin disorder in the family or immediate environment, and no close contact with those with skin disorders should be allowed for 21 days afterwards (Reynolds and Joos 1958) Reactions should be covered to prevent accidental contamination of others, and it should be made clear that for a vaccination reaction to be left uncovered at least until the scab has separated is dangerous to others Conversely, those with skin disease should be aware of the danger of contact with the vaccinia virus Because atopic eczema rarely appears before 3 months of age, the children of families with atopic histories should be vaccinated at 2–3 months (Reynolds et al. 1958), for vaccination at this age has proved effective (Doorschodt 1957)

With the simple precautions described above the case reported here would not have arisen, and the incidence of eczema vaccinatum could be reduced.

I should like to thank Dr H J Wallace and Dr B D R Wilson for permission to publish this case, Dr J E Cullis for helpful criticism and advice, Dr Donald Teare for the postmortem examination, the photographic department of St Thomas' Hospital for the photographs, and Dr F O MacCallum and Dr J C MacDonald of the Virus Reference Laboratory, Colindale, for the postmortem virological and bacteriological studies, and for supplying the hyper-immune gamma-globulin

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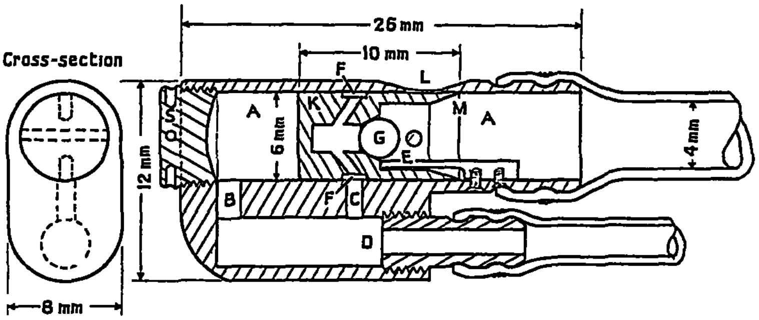
New Inventions

MULTIPLE-RETRIEVING SMALL-INTESTINAL BIOPSY TUBE

SUCTION biopsy of the gastric mucosa, first devised by Wood et al,[1] has been employed in many centres More recently the same principle has been used for biopsy of the small-intestinal mucosa Shiner[2] described an instrument which was essentially the same as the Wood tube but slightly more flexible and longer Other valuable modifications have been made, particularly the "multipurpose" instrument of Brandborg et al,[3] the "intestinal biopsy capsule" of Crosby and Kugler,[4] and the tube designed by Henning et al[5] The last two instruments differ from the Shiner tube in that a wire no longer passes down the tube to operate the knife, and so the flexibility is increased

To obtain multiple mucosal specimens from different levels of the small intestine, it is essential (1) that the biopsy instrument should be flexible enough to pass along the small intestine, (2) that the instrument should be capable of taking multiple biopsy specimens, and (3) that it should be possible to tell from which level the biopsies came Although Shiner's tube and the tube described by Henning et al are capable of taking multiple specimens, these become mixed up within the cutting head, and on withdrawing the instrument the specimens cannot be sorted into their appropriate levels The Crosby biopsy capsule can be fired only once, having then to be withdrawn, reset, and passed again



The tube we describe was designed to overcome these defects It will pass well down the small intestine, taking any number of pieces of mucosa and delivering them to the operator as they are cut, thus revealing the level from which they came

THE INSTRUMENT

The cutting head (26 × 12 × 8 mm) is composed of a cylinder, A, fed by ports B, C, and D (see figure) The cylinder, of 6 mm internal diameter, contains a lateral hole, L (diameter 2 5 mm), through which the mucosa is sucked The bottom end of the cylinder is closed by a capstan screw, S, and the proximal end is attached to a polyvinyl tube of 4 mm. internal diameter and 2 m long The port, D, is connected to a radio-opaque polyethylene tube of 1 mm internal diameter and 2 m. long The knife, K, is a hollow piston 10 mm. long with a sharp leading edge, M A narrow channel, F, encircles the knife about midway down its length, and from this channel holes pass obliquely into the interior Within the knife is a non-return ball valve, G, which allows fluid to pass from the channel, F, into the centre of the knife The cylinder and the knife are lapped together to a perfect sliding fit The movement of the knife beyond the lateral hole is arrested by a stop, E

The two tubes are bound together at 30 cm intervals The distal end of the narrow tube is fitted with a Luer adaptor which is then attached to one arm of a standard metal three-way tap, the second arm is connected to a source of negative pressure of 50 cm Hg, and the third arm to a 100 ml Luer-lock syringe

TECHNIQUE

When a negative pressure is applied to the back of the knife via port B and the narrow-bore tube, the knife is sucked back, thus opening the lateral hole, L, and closing the port, C With negative pressure still applied to the narrow-bore tube, a lesser negative pressure is applied to the wide-bore tube by means of a 30 ml syringe This sucks in a knuckle of mucosa through the lateral hole, L Via the three-way tap, the negative pressure on the narrow-bore tube is rapidly changed to positive by compressing a 100 ml. syringe filled with fluid This positive pressure is transmitted down the narrow-bore tube, through the ports D and B and to the back of the knife, which moves rapidly forward cutting off the mucosa sucked through the hole, L When the knife is fully closed it rests against the stop, E, and, as in the figure, the channel, F, comes opposite the port, C, the fluid passes through C into F, and thence through the small holes into the centre of the knife The ball valve, G, then opens, allowing the fluid to pass through the knife into the wide-bore cylinder, A, and up the tube This flushes the specimen of mucosa up the tube and delivers it at the proximal end

To reset the knife, negative pressure is again applied to the narrow-bore tube, and transmitted through C into the channel, F, and so to the interior of the knife This closes the ball valve, and allows a negative pressure to be exerted behind the knife. The knife is then sucked backwards to the fully open position closing off the channel, F That the knife is open can be confirmed by applying a small positive pressure on the wide-bore tube, if the knife is open, no resistance will be felt

When tested on the bench with freshly removed small intestine or stomach, it can be shown that every time mucosa is sucked into the lateral hole, L, it can be cut off by the knife and delivered at the upper end of the tube If no specimen is delivered, then no cut has been made The only exception is that very occasionally the specimen may become stuck in the cutting head Therefore if, in vivo, no mucosa is delivered, the knife should be opened and quickly closed again, and the tube washed through with a further 100 ml of fluid, when the specimen will be dislodged and carried up

The size of the specimen depends on the degree of negative pressure applied If the pressure is insufficient no mucosa may enter the lateral hole, L On the other hand if the pressure is too great, there is a theoretical possibility of perforating the intestine In practice we have found that suction with a 30 ml syringe produces adequate negative pressure without making the cut too deep

RESULTS

The tube has now been used in 36 cases, and in 34 satisfactory biopsy material was obtained from the small intestine. In 32 cases multiple specimens were taken from different levels of the jejunum, duodenum, and stomach, without complications

The advantages of this tube considerably increase the

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tential value of intestinal biopsy in the study of the rphology and function of the intestinal mucosa

We are grateful to many friends for help and encouragement anks are especially due to Dr. Ian Wood of the Walter and Eliza ll Institute, Melbourne, to Prof A. C Fraser and Mr Norman tes of the department of pharmacology and medical biochemistry mingham, and to the manufacturers, Messrs H A Taylor & n, Melbourne, for their help and skill in making the final strument

Wellcome Research Unit,
Christian Medical College,
Vellore, South India
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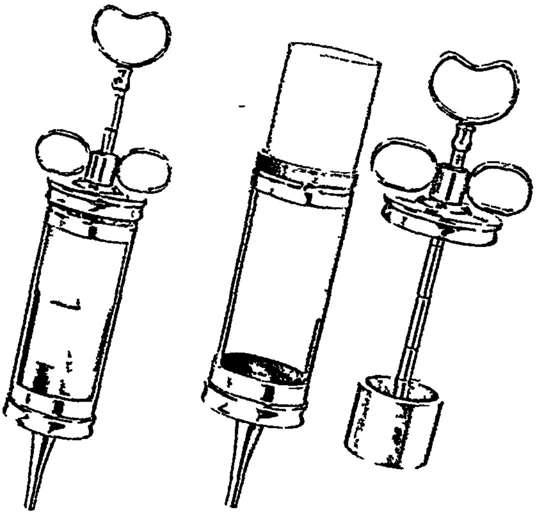
A NEW BLADDER SYRINGE

Those who use a bladder syringe are well aware of the dvantages of an instrument with a glass barrel with a metal unger The Riches bladder syringe, the best-known of this nd, has given good service It has the disadvantage, however, at the barrel may be broken, and when this happens the pair is costly and often takes much time because of the cessity to cement the barrel into the metal mounts To ercome this disadvantage a bladder syringe has been signed which is basically similar in pattern to the Riches ringe, but has replaceable barrels and pistons (see figure)



A glass barrel, with its own fitting piston, slides between rigid metal side members and rests on carefully fitted rubber washers at the nozzle mount and at the top cap The syringe is reassembled after sterilisation, and when the top cap is screwed into position a water and airtight fit is achieved.

With reasonable care this syringe has proved as efficient as the original Riches pattern, and it has the following advantages

1 The initial cost is low

2 The cost of replacement of barrel and piston is less than that of repairing and recementing a Riches-pattern syringe

3 The risk of breakage during sterilisation is small, since the barrel is free in its mounting and the differing coefficients of expansion of metal and glass become unimportant

4 The metal frame helps to protect the barrel from impact fracture

5 A broken barrel can be replaced immediately from a supply of spares kept in the hospital

This instrument has now been used for about 6 months at All Saints' Hospital, and has proved very satisfactory A modicum of care is required in assembly, but otherwise no difficulties have arisen in its use.

The syringe is available from Allen & Hanburys, Ltd, 48, Wigmore Street, London, W 1, from one of whose representatives the idea originated I should like to thank them for help in the design and manufacture

All Saints Hospital,
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Robert Cox
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A NEW TYPE OF ANGLED-CATCH FORCEPS FOR ANTERIOR COLPORRHAPHY

In correcting minor degrees of urethrocele and cystocele, or in making the vaginal approach for a sling operation, particularly where there has been a previous anterior colporrhaphy, the anterior vaginal wall has to be opened up under circumstances which can be difficult with the usual straight-catch forceps These jut out towards the operator, hinder his movements, and are liable to become entangled with catgut, needle-holder, or some other instrument

To overcome the difficulty and at the same time to give better access to the anterior vaginal wall, a Littlewood's catch forceps has been angled as shown in fig 1 When in use (fig 2) the shaft and handle of this forceps lie close against the perineum, offering no obstruction to the operator

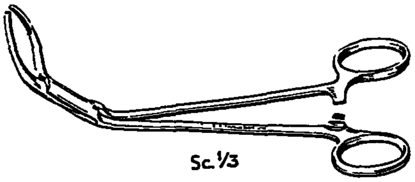


Fig 1

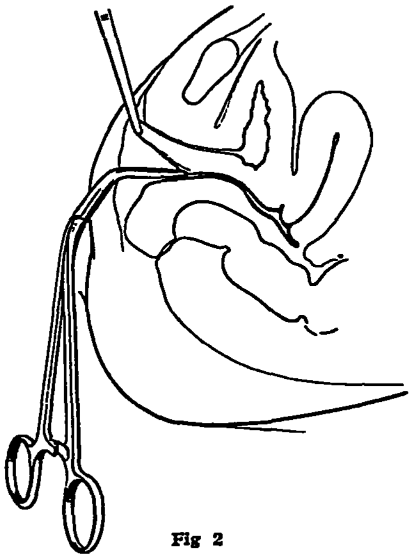


Fig 2

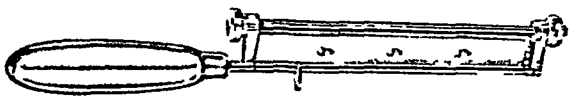
This instrument is made by Charles F Thackray Ltd, 10, Park Street, Leeds, 1

Royal Victoria Infirmary,
Newcastle upon Tyne, 1
J K Russell
M D Aberd, F R C O G

A SKIN-GRAFTING KNIFE

Although conventional hand knives, designed to cut split-thickness skin-grafts at a predetermined depth, have been brought to a high degree of efficiency, they still have tiresome disadvantages If a rotating roller is used to regulate the depth of cut the graft often tends to adhere to the roller, particularly when very thin skin is taken, an assistant must therefore adjust the skin over the knife blade with forceps, with consequent risk of tearing Moreover the roller must slide to and fro along its long axis, necessitating slack end-bearings which reduce precision in the setting, hence the graft sometimes becomes gradually thicker as the knife progresses Usually two adjustments are necessary at either end of the knife to set the depths of cut, if these are set unequally the graft will be thicker at one side than the other

The knife here described overcomes these difficulties without the need for complex mechanical parts The principle involves the use of a polished-steel rod for regulating the



depth of cut, this rod has no independent movement, either sliding or rotation, whilst the graft is being taken At its end-bearings it passes eccentrically through the bushes, hence the depth of cut can be set by rotation of the rod with a single knurled control knob, the rod remaining parallel to the blade at all settings With this arrangement the bearings can have a precision fit, and there is no "play" in use Whilst cutting the graft, spontaneous rotation of the rod is slight, but a locking lever is provided to avoid accidental alteration of the setting once it has been made The knife edge is of the disposable razor-blade type

This knife is simple to handle, and it will cut thin Thiersch grafts consistently and with precision

The knife may be obtained from Allen & Hanburys Ltd, 48, Wigmore Street, London, W 1

Queen Victoria Hospital,
East Grinstead, Sussex

JOHN WATSON
M A, M B Cantab, F R C S E

Reviews of Books

Anatomy: a Regional Study of Human Structure

ERNEST GARDNER, M D, Wayne State University, DONALD J GRAY, PH D, Stanford University, RONAN O'RAHILLY, M SC, M D, Wayne State University Philadelphia and London W B Saunders 1960 Pp 999 105s

ANATOMISTS always find new textbooks interesting, if only because there is widespread dissatisfaction with the ones available This dissatisfaction springs largely from wide variation in views about what *should* be taught to medical and other students and how Each teacher seems to have different views, hence the steady stream of new books, few of which receive general acceptance This new book may, however, be an exception Though it contains much of the traditional lore, arranged on a regional basis, tediously exact and explicit description of many structures has been avoided On the other hand, some readers may think that too much "applied" anatomy has been sprinkled through the text, with a garnishing of allusions to embryology, comparative anatomy, and function But it is this very introduction of non-structural considerations, closely woven into the dead weight of topography, which gives this book its individuality and attraction The task has been fulfilled with skill, and the result is a readable book, offering the novice a far more lively and balanced aspect of anatomy than is usual

Apart from the first hundred pages, which give a general introduction to bones, joints, muscles, nervous system, vessels, viscera, skin, development and growth, and radiological anatomy (a superb chapter), the text ambles gently through the body with sufficient references for all but the expert It is a pity that the central nervous system and embryology were omitted, surely the current view that two other large tomes are needed for these "specialties" is questionable

The illustrations are all line drawings or diagrams Their quality varies, but they are many and helpful, and never claim to be a substitute for the dissecting-room In sum, this is a work which should receive at least a trial in every department

Cerebral Dominance and its Relation to Psychological Function

O L ZANGWILL, M A, professor of experimental psychology, University of Cambridge, visiting psychologist, National Hospital, Queen Square, London Henderson Trust Lecture no xix Edinburgh Oliver & Boyd 1960 Pp 31 10s 6d

IT seems from this very physiological lecture that the link between handedness and cerebral dominance is not at all clear for left-handed people Professor Zangwill, whose neurological orientation is well known, suggests that the left hemisphere is more often dominant in such people than the right, and that some show imperfect lateralisation Speech function, too, is less clearly located in these people and recovery from aphasia is more complete traditional concepts of language localisation only apply, according to Zangwill, in right-handed people of dextral stock 20 cases of dyslexia studied at Queen Square showed a link with "cereb ambilaterality" and the suggestion is made that such peop have a tendency towards temperamental instability and vu nerability to stress Professor Zangwill sees cerebral dominan as a graded characteristic, varying in scope from person person, especially among the left-handed

Radiology as a Diagnostic Aid in Clinical Surgery

HOWARD MIDDLEMISS, M D, F F R, D M R D, director of radi logy, United Bristol Hospitals London Heinemann Medi Books 1960 Pp 151 30s

RADIOLOGY is so much a part of a surgeon's life that fe stop to question their own knowledge of it it is not until t subject is set out in the clear and concise terms which D Middlemiss has achieved that unsuspected gaps are expose He has set about the task of enlightening the surgeon eith by refreshing his memory or by bringing him up to date in admirable manner, each diagnostic manœuvre is consider in its application, then method, and finally the findings a their interpretation The book starts with emergencies, pass to postoperative conditions, and then covers the remain territory anatomically in six more chapters The reproductio are first-class as must have been the originals chosen a doubtless created by Dr Middlemiss himself This is sensible book with a kindly word of warning to the surge in the last chapter about the effects of irradiation on hims and those around him when, for example, undertaking oper tive cholangiography This chapter appropriately includes note of caution on the patient's behalf—a note which cou to advantage have been sounded at the outset and more loudl

African Homicide and Suicide

Editor PAUL BOHANNAN, associate professor, department anthropology, Northwestern University, Chicago Princeto New Jersey Princeton University Press London Oxfo University Press 1960 Pp 292 18s

Dr Bohannan has turned to the neglected subject of com parative criminology to show the effects on the patterns murder and suicide of tribal customs and social organisation seven African peoples In the first chapter, he examines th theories about homicide and suicide, pointing to the relati neglect by sociologists and anthropologists of the study homicide and comparing this with the concepts of Durkhei Malinowski, Westermarck, and others on suicide The ne seven chapters consist of essays, based on the official loc records, on homicide and suicide among seven African peoples the Tiv of Central Nigeria, the Basoga, the Gisu and th Nyoro of Uganda, the Luyia and the Joluo of Kenya, and th Alur of north-west Uganda Dr Bohannan himself contribute the chapters on the Tiv and the Luyia peoples, and the othe chapters were written by other anthropologists Detaile illustrative cases show the type of homicide or suicide charac teristic of each tribe, and those which are unusual

In a final chapter on the patterns of murder and suicid revealed by the survey, Dr Bohannan draws attention to th influence of tribal and kinship organisation, belief in witch craft, and economic factors such as competition for land i determining the commonest type of murder or suicide Stud of the role of killer to victim, or the role in which an individua commits suicide, can throw useful light on the stresses within community, and Bohannan favours this approach rather tha the psychological theories of "motive" Tables and a appendix summarise the data

Advances in Pediatrics (*Volume XI* New York Yea Book Publishers London Interscience Publishers 1960 Pp 285 68s)—This series has won a reputation for quality in selection, presentation, and production, but this year s selection of subjects is disappointing Respiration, for instance, has lately been reviewed elsewhere, and the chapters on allergy and iminoacidurias add little new information But the chapter on the effects of sodium imbalance on the central nervous system is stimulating, and the review of infantile diarrhoea offers new insight into old problems and shows that enthusiasm and ingenuity are still needed in pediatrics

THE LANCET

LONDON 24 SEPTEMBER 1960

Casualty Departments

THE Nuffield Provincial Hospitals Trust publishes this week a report on Casualty Services and their Setting[1] This describes a survey of fourteen areas, with twenty main hospitals and several smaller ones, serving a population of some 5 million The committee[2] sent a clinical team to visit the areas and the casualty departments in them, and their report includes an estimate of how well the various departments fulfilled their own conception of what casualty departments should do, observations on the quality of medical staffing, accommodation, and equipment, and some suggestions on how future assessments of casualty department work could be made Though brief, it is the most comprehensive examination of this part of the hospital service that has yet appeared in print Not only the medical but the clerical and secretarial parts of the close-knit team may congratulate themselves on a profound study and a powerful challenge

On p 698 we publish the main conclusions and recommendations The low priority of the subject in schemes of reform is traced mainly to the poor status of casualty work and to the imprecision of the term "casualty" The committee, however, avoid prescribing general remedies, and urge regions to examine their own casualty services and accumulate detailed information before making decisions on the improvements in staffing, organisation, and buildings which will unquestionably be indicated We could have expected severe criticism of some of our older departments, and we get it What is more disturbing is the committee's disapproval of some of the departments which have been recently reorganised and rebuilt with the reforms they advocate already in mind

Conclusion 10 says "In view of the poor accommodation in the newer departments visited, it is strongly recommended that the functional requirements of casualty departments should be carefully studied in conjunction with all practising personnel, and the results applied in new buildings, as well as in the adaptation of existing accommodation" A comment on a recently opened new department speaks of "first-class medical staff who are providing an enlightened accident service in spite of the drawbacks of planning mistakes and faulty engineering services" Of another department, built three years ago, they remark "the corner of this room is rather a grim sight", and again, "in 1956 at a cost of £7000 to £8000 an extension was built The design is very poor and has done nothing to enhance the department"

These quotations should, of course, be placed in their proper context, and what the committee approved of in the same departments should be remembered too But whether everyone will remember it is more than doubtful, for the report is on the bookstalls, and extracts are already in the lay press Lay, and political, interest in the deficiencies of the casualty services is increasing as rapidly as medical interest, and the suggestion that those who organise these services have already set off in what may be a wrong direction needs attention Other stimulating topics touched upon include the status and prospects of senior casualty officers, the belief that in any casualty department the services of a consultant should be immediately available throughout the twenty-four hours of the day, the dangers of cross-infection, and contact between casualty departments and rehabilitation and industrial replacement facilities Among the conditions fundamental to the arrangements for urgent accident and emergency cases is one which we shall all be glad to endorse as soon as we can—"full twenty-four-hour cover by doctors adequately trained for the work they are called upon to do, and who are assured of the stability and importance of this phase of their medical career"

Though the report is entitled "Casualty Services and their Setting", the greater part of it is devoted—and very successfully devoted—to casualty departments themselves It is true that references are made to industrial medical services, and statements such as "relations between family doctors and this hospital seem uneasy" occur in places Nevertheless the problems of the cases returned to their own doctor, the impact of one hospital's work on that of its neighbours, the disposal of individual patients in a network of specialties and a multiplicity of hospitals, and the responsibilities of such as the ambulance service in directing unscreened acute cases—all these need much more detailed consideration if a balanced picture of the situation is to be given They may not form the greater part of the work of casualty departments, but they do provide most of the dilemmas for casualty officers, and a high proportion of the causes of complaint They would justify an equally extensive survey all to themselves

We have picked out some of the points which may give rise to surprise and controversy, but they do not reduce our respect for the report, for the committee which prepared it, or for the Trust which inspired and financed it—nor our relief that the "need for leadership and urgent executive action" should now be so firmly pointed out We are informed that those departments and administrative bodies throughout the country which cooperated did so with special enthusiasm, and that the sympathetic encouragement they were given by the visitors has had a lasting effect The most charming and most generally appreciated observation was made on the quality of the senior nursing staff "It was notable that in every hospital the team agreed that the standard of the sister in charge of the casualty department was extremely high In many cases it would not be an exaggeration to say that the sister was really the lynch-pin of the department " Nothing could be truer than this, and perhaps nothing could be better But it is definitely not enough

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[1] Casualty Services and their Setting a Study in Medical Care London Oxford University Press, for Nuffield Hospitals Trust 1960 Pp 135 7*s* 6*d*

[2] The steering committee consisted of Dr John Fry (chairman), Mr J N Barron, the late Sir Ernest Rock Carling, Mr Norman Lake, Dr R F L Logan, Mr L W Plewes, and Mr Gordon McLachlan (secretary) The surveyors who made the field observations were Mr Lake, Mr Barron, Dr Logan, and Mr Plewes

Systemic Lupus Erythematosus

Systemic lupus erythematosus has been known for many years, but its ætiology is still not clear It is diagnosed more often now because the " L E -cell phenomenon " has provided a test which is diagnostic in most cases, and because combinations of steroid and other treatment have offered methods of control Views on ætiology reflect passing fashions in medicine Thus at first it was termed " toxic ", then it was ascribed to an infection probably linked with tuberculosis, and latterly it has been grouped with the "collagen diseases" Dameshek[1] suggested that systemic lupus erythematosus fitted in better with the immunological diseases He pointed out that many immune types of disturbance were known to occur in systemic lupus erythematosus, particularly blood disorders such as auto-immune hæmolytic anæmia and thrombocytopenic purpura, in addition, false-positive serological tests for syphilis, and occasionally leucopenia and disturbances of blood coagulation, might be found

The difficulty with the immune hypothesis has been to explain why autoantibodies develop in an apparently healthy person and why they produce such diverse effects Dameshek[2] has now drawn attention to the rather similar state which develops when bone-marrow " grafts " are inserted into a host whose own immune reactions have been temporarily inactivated by a large dose of radiation In these circumstances the *host's* antigens stimulate the production of antibodies by the cells in the graft which are still immunologically competent, these autobodies may then attack the cells of the host, and the resulting syndrome has been variously known as runt disease, homologous disease, or secondary disease Loss of weight, skin disturbances, intractable diarrhœa, grave anæmia, or leucopenia have been found in this disease, and clearly several systems can be affected How the abnormal cells first arise in the host is unknown, but the possibility that they may cause disease has occurred to several workers Burnet,[3] for instance, suggests that " forbidden clones " appear in systemic lupus erythematosus

The idea of abnormal cells gradually involving more systems fits in with our changing ideas on the clinical course of the disease The standard description of systemic lupus erythematosus is of a rapidly progressive disease of one or two years' duration with fever, skin lesions on the face and often elsewhere, swelling of small joints, splenomegaly, and sometimes hepatic lesions, endocarditis, and finally renal failure Application of the L E -cell test has shown that many patients have a relatively mild illness, surviving for several years during which new symptoms from involvement of previous healthy systems appear from time to time. The difficulty here is to make the diagnosis, since the L E -cell test may be negative if the responsible abnormal protein has not developed But tests for the L.E.-cell phenomenon have been greatly improved and even a finger prick technique has been devised[4] According to Dubois,[5] of Los Angeles, the test is positive in 80% of cases of systemic lupus erythematosus, though repeated testing over many months may be needed in some cases False positives arise only in some cases diagnosed as rheumatoid arthritis, and in the long run these may turn out to be cases of lupus Other tests are not so specific In the 20% of cases with a negative L.E -cell test a combination of several clinical signs, such as a discoid lupus rash, involvement of small joints, false-positive syphilis tests, or typical blood-vessel changes in a skin biopsy, is sufficient Dubois states that, in his series of 400 cases, 10% had to be diagnosed on clinical data alone and in another 10% skin biopsy confirmed the diagnosis

The change of view about the clinical severity of the disease should influence treatment At present this consists in bed rest and administration of three sets of drugs—salicylates, antimalarial drugs, and steroids. Dubois,[5] having reviewed his methods of treating a large group of cases, concludes that the discovery of a few L E cells or a false-positive serological test in a patient with none of the recognised symptoms should not be the signal for steroid treatment, no treatment is needed till symptoms appear If the symptoms are rheumatic—joint swellings with some fever—bed rest and full doses of salicylates are often sufficient If salicylates fail, or if skin lesions appear, the next line of attack is to give antimalarial drugs Dubois usually chooses hydroxychloroquine ('Plaquenil'), 200 mg three or four times daily, since no serious side-effects have been reported He applies steroid therapy only if salicylates and antimalarials fail, or if the patient is critically ill, or if there is neurological or renal involvement For the relatively mild case he recommends adding a small dose to the combination of salicylates and antimalarial drugs—say, up to 50 mg cortisone or 10 mg prednisolone daily If the symptoms are not controlled, the dose should be raised in steps, by perhaps 20% weekly, and then decreased in the same way when control has been attained If more than 50 mg cortisone daily (or the equivalent of the newer steroids) is needed, treatment against the development of peptic ulceration should be given—i e, six meals a day, antacids, and anticholinergic drugs With seriously ill patients, steroids in large doses are given from the first, salicylates and antimalarial drugs are not used A dose of 400 mg. cortisone (100 mg prednisolone) is a good starting figure, and it can be adjusted up or down as needed, cortisone in doses of up to 4000 mg daily has been needed to control acute crises Dubois suggests that if steroid treatment has not brought relief in two months, a course of nitrogen-mustard injections should be given.

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[1] Dameshek, W *Ann intern Med* 1958, 48, 707

[2] Dameshek, W *Arch intern Med* 1960, 106, 162

[3] Burnet, M *Brit med J* 1959, ii, 720

[4] Lempert, H, Berlyne, G M *ibid* 1957, i 1041

[5] Dubois, E L. *J Amer med Ass* 1960 173, 1633

The best guides to the control of steroid therapy are the clinical picture and the hæmoglobin level, if the kidneys are involved, tests of renal function should be repeated at intervals The erythrocyte-sedimentation rate is not helpful since it often remains raised after complete clinical remission, and the L.E.-cell test is too slow to change to be useful for controlling treatment

Dubois has compared the action of several steroids in his cases 50 patients were treated with dexamethasone and compared with similar groups treated with methylprednisolone, triamcinolone, and prednisolone or prednisone Dexamethasone is twenty times as powerful as hydrocortisone and eight times as potent as methylprednisolone It does effectively control systemic lupus erythematosus, but unfortunately it is considerably more liable to produce side-effects than its less active predecessors For example, œdema occurred in 28% of patients treated with dexamethasone compared with 6% of those on the prednisteroids, 60% developed a cushing-like appearance and 28% hirsuties, compared with 49% and 3% respectively for those on prednisteroids Triamcinolone produced a curious muscle weakness,[6] but dexamethasone and the other steroids did not cause this symptom **Dubois** thinks that the improvement in the blood-count was less with dexamethasone than with the others, and he was also troubled with variation of individual response to this drug He concludes that, for acute attacks, initial treatment with hydrocortisone is best, and for other cases, including those with renal complications, prednisone or prednisolone is still to be preferred

One of the dangerous complications of systemic lupus erythematosus is the appearance, often acutely, of an auto-immune type of hæmolytic anæmia, various estimates put the incidence at between 3 and 10% In most patients full doses of prednisolone—say, 100 mg daily—will control the attack, and the hæmoglobin level can be restored by blood-transfusion But in some patients steroids are not effective, and then the question of splenectomy arises **Wasserman** et al [7] treated 2 such cases by this operation, in 1 the result was fair, but in the other no improvement ensued **Sarles** and **Levin** [8] have reported that splenectomy was successful in 3 cases which were not controlled by steroids, eight months later 1 patient was receiving no treatment, and 2 were controlled by moderate doses of steroids Clearly the operation should be reserved for the few patients who have not responded to other treatment The scheme of treatment outlined by **Dubois** indicates the importance of not administering steroids too soon in mild cases, and the equal importance of giving really effective doses of steroids at once in acute cases Owing to the increasing recognition of milder cases, systemic lupus erythematosus can no longer be regarded as a rare disease in the Los Angeles County General Hospital it is almost as frequent as leukæmia, rheumatic fever, serum sickness, or pernicious anæmia So most physicians can expect to have to deal with this disease fairly often

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[6] See Williams R. S *Lancet* 1959, i, 698
[7] Wasserman, L. R., Stats, D , Schwartz, L., Fudenburg, H. *Amer J Med* 1955, 18, 961
[8] Sarles, H E., Levin, W C *ibid* 1959, 26, 547

The Riddle of Tropical Sprue

The new methods of obtaining fresh tissue from the intestinal tract have opened up a new approach to the physiology of the intestinal cell and disorders of the gut. Using the principles established by **Wood** et al [1] and **Tomenius** [2] for biopsy of the stomach, **Shiner** [3] followed by **Crosby** and **Kugler** [4] and **Rubin** [5] have each produced instruments with which one to three biopsies may be taken at a time **Rubin** et al [6] have now devised a method which may take 25–30 biopsies at a session at any place from the ileocæcal valve to the duodenum, and in our present issue Dr **Baker**, of Vellore, and Mr **Hughes**, of Melbourne, describe another valuable instrument, providing serial sections **Astaldi** and **Strosselli** [7] have studied the normal jejunum in great detail, and gradually the normal histological picture of the ileum is also being depicted Enzymatic and histochemical studies are beginning to reveal something of the complex metabolic processes taking place in the intestinal cell alongside the essential process of absorption Large numbers of patients with cœliac disease, idiopathic steatorrhœa, and tropical sprue have now been studied, and definite histological changes in the intestinal mucosa have been demonstrated, though the nature, degree, and extent of intestinal involvement cause debate

Manson-Bahr [8] has lately pointed to the contrast with the early work on tropical sprue, in which the occasional patient was studied at necropsy after a long and debilitating illness But among these early observations on the pathology of the intestinal tract there was much that has been found now to be true

Sprue was first described as a separate entity by **Manson** [9] in 1887 in Annam and **van der Berg** [10] in 1887 in Java **Manson** thought that the small intestine was atrophied, while **van der Berg** held that gastric catarrh was the essential lesion, and that atrophy of the intestinal walls and the liver was secondary Changes in the small intestine were noted by **Thin**,[11] **Wethered**,[12] **Faber**,[13] **Justi**,[14] and **Begg** [15] Consistent findings were shortening of villi and infiltration with round cells and plasma cells, while ulceration of the ileum was common. Thinning and distension of the intestinal wall was often noted, as might now be expected in patients chronically dehydrated and electrolytically depleted Needless to say, there were two schools of thought—one that the lesions were a principal factor in the disorder and the other that they were the results of postmortem autolysis

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[1] Wood, I J , Doig, R K., Motteram, R., Hughes, A. *Lancet*, 1949, i 18
[2] Tomenius, J *Gastroenterology*, 1950, 15, 498
[3] Shiner, M *Lancet*, 1956, i, 17
[4] Crosby, W H , Kugler, H W *Amer J dig Dis* 1957, 2, 236
[5] Brandborg, L L., Rubin, C E., Quinton, W E. *Gastroenterology*, 1959, 37, 1
[6] Flick, A L , Quinton, W E., Rubin, E. C Communication to American Gastroenterological Association, 1960
[7] Astaldi, G , Strosselli, E *Amer J dig Dis* 1960, 5, 175
[8] Manson-Bahr P H *J trop Med Hyg* 1960, 63, 49
[9] Manson, P China Imperial Maritime Customs Medical Report, 1887, p 33
[10] van der Berg, C L. Indische Sprue (Aphthæ tropicale) Batavia, 1887
[11] Thin, G Psilosis or Sprue its Nature and Treatment. London, 1890
[12] Wethered, F J *Trans path. Soc Lond* 1891, 42, 116
[13] Faber, K. *Arch Verdaukr* 1904, 9, 333
[14] Justi, K. *Beiheft Arch. Schiffs-u Tropenhyg* 1913, 5, 394
[15] Begg, C. Sprue Its Diagnosis and Treatment. Bristol, 1912.

A major contribution was made in 1915 by Bahr[16] who, though he then thought that sprue was probably caused by infection with thrush fungus, pointed out that clinically the disease may take distinct forms according to the portion of the alimentary tract involved He gave a good description of the changes found in the ileum of two Europeans who had died of tropical sprue in Ceylon

"The villi are quadrangular in shape and shrunken, the columnar surface epithelium for the most part preserved, but the cells stain badly and the nuclei can with difficulty be distinguished Chronic inflammatory changes are evident, the capillaries are congested and the interstitial tissue is packed with small round cells and larger cells (leucocytes and plasma cells), the vessels of the submucosa are greatly dilated, there is general fibrosis and the goblet cells at the fundus of Lieberkuhn's crypts are distended There is some evidence that the muscular coats have been affected by the same inflammatory condition"

In 1924 Manson-Bahr[17] described two further necropsies on adults who had died in temperate climates, concluding that intestinal ulceration was a primary factor in the pathology In 1929 Mackie and Fairley,[18] from Bombay, laid stress on the difficulties of assessing the pathological findings when working on postmortem material in hot climates without cold storage They too described "withering of the villi" and supported Manson-Bahr's contention that the cause of tropical sprue was to be found in the intestinal tract In 1932, however, Thaysen[19] summarised the previous reports and his findings in non-tropical and tropical sprue "The organs have shown only some insignificant changes and the pathological changes demonstrated are to be taken as secondary phenomena produced by malnutrition, anæmia and perhaps intoxication from the intestinal canal" His opinion carried weight far in excess of the rather inadequate data put forward to support it, and it was generally accepted for twenty-five years Even Fairley[20] in 1936 retracted somewhat from his earlier publication, and after failure to find "withering of the villi" at necropsies performed in London came to believe that the findings were the result of autolysis In 1941 Manson-Bahr[21] defended the hypothesis that abnormalities of the small intestine were the basis for tropical sprue, and now the new techniques have made histological examination easy and have proved the presence of changes But as so often happens, in answering a few questions they have posed many more Are the changes the result of infection and are there numerous causes? Are they the same as non-tropical sprue, and are they related to cœliac disease? Are they caused by dietary defects and is there, even in tropical sprue, a constitutional enzymatic defect in the intestinal cell? It is long since Sir Philip Manson-Bahr set himself to answer some of these questions, but even now his "riddle of tropical sprue" remains something of a riddle

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[16] Bahr, P H A Report on Researches on Sprue in Ceylon. London, 1915

[17] Manson-Bahr, P H *Lancet*, 1924, i, 1148

[18] Mackie, F P, Fairley, N H *Indian J med Res* 1929, 16, 799

[19] Thaysen, T H Non-Tropical Sprue London, 1932

[20] Fairley, N H *Trans R Soc. trop Med Hyg* 1936, 30, 9

[21] Manson-Bahr, P H *Trop dis Bull* 1941, 38, 123

Purer Food

This week's conference and exhibition in London to celebrate the centenary of the first Food and Drink Act points the contrast with the state of affairs only a century ago It has become difficult to imagine the apathy and ignorance of the general public a hundred years ago regarding the food they ate or the medicine they swallowed, or to conceive of the unscrupulous, deliberate adulteration practised by some traders Except for sporadic attempts to detect, and devise punishments for, specific instances of adulteration, the sophistication of basic foodstuffs and drugs was accepted as part of the natural order of things, and its ill effects were taken for granted The first determined effort to make the truth known in this country was made by a German named Accum, who came to London in 1793 with some pharmaceutical and chemical knowledge, and finally, with the help of King George III's apothecary and others, set up a small chemical laboratory and built up a considerable reputation as consultant and lecturer His greatest interest was in the composition of foods, and his analyses of hundreds of samples of ordinary articles of diet were finally published in 1820 under the title of *A Treatise on Adulteration and Culinary Poisons* The cover was appropriately decorated with a design of a spider in a web about to devour a fly, surrounded by intertwined serpents with a skull and crossbones on top Underneath was a quotation from the 2nd Book of Kings "There is Death in the Pot" In his book Accum described some of the iniquitous practices of his time—for instance, the almost universal addition of alum to flour and bread, the reinforcement of beer by ferrous sulphate, and of gin by sulphuric acid, the adulteration of coffee with chicory and of mustard with capsicum, and the use of salts of copper, lead, and arsenic for colouring The appearance of this book, which ran into four editions in two years, raised a tremendous outcry Unfortunately for Accum, he also published the names and addresses of culprits, and these and others of the same malignant species were able, largely owing to Accum's own imprudence, to convict him on a trivial and entirely irrelevant charge of mutilating books belonging to the Royal Institution As a result, the public lost confidence in what he had written, and by 1824 the national alarm had almost subsided One or two abortive attempts were made in the next twenty years to revive the memory of Accum's work, but eventually it was the founder and first editor of *The Lancet*, Thomas Wakley, who initiated the campaign which ultimately roused a lethargic Government to legislative action

In 1850 he appointed Dr A H Hassall, an eminent microscopist, who had already published papers on the detection of chicory in coffee and of impurities in sugar, and Dr Henry Letheby, a lecturer in chemistry at the London Hospital Medical College, as members of *The Lancet*'s Analytical Sanitary Commission. His proclaimed intention was "to enquire into and report on the quality of solids and fluids consumed by all classes of the public", and he entered the conflict ith a full sense of the responsibility of his undertaking

The first report on the Commission's activities ppeared in *The Lancet* in 1851 and was concerned with offee It disclosed, among other things, that of 213 amples bought in London 184 were adulterated At he end of three months the names and addresses of he merchants implicated were published, a clamorous utcry arose, particularly as some of the accused had ought their supplies in good faith The reception of he venture by the lay press, led by the *Times* and the *Manchester Guardian*, was cordial *Punch* published a eries of articles in which the malpractices of food dealers were described by such words as "fraudulent", 'scoundrel", "rascality", and "swindle" One ively article described the "imps" of the food trade, among them "the grocer-imp, who enriches his chocolate with brick dust and with a morning draught conveys the materials of a vault", "the baker-imp who grinds his alum to make his bread and selling the staff of life, makes the staff carry a mischievous weapon for the bowels of those who trust to it", and "the publican-imp whose ale is sharpened with the fiery edges of vitriol"

For four years *The Lancet* continued to publish its articles HASSALL's analytical methods were far in advance of any previously known, and his extensive use of the microscope brought to light many scandalous actices The whole of the work was published by ASSALL in 1855 and created a deep impression on the iblic mind In fact, the extent of adulteration decreased onsiderably over this period The opportunity for ergetic action was this time not allowed to slip *he Lancet* pressed the Government for the appoint-ent of a Select Committee to consider the whole uestion of food adulteration, and as a direct conse-uence the first Food and Drink Act in this or any other untry was passed in 1860

The Act was certainly far from perfect It permitted, ut did not compel, the appointment of official analysts y local authorities, and owing, on the one hand, to the endency of human beings to do no more than they ust, and, on the other, to the fact that many local ouncils were largely composed of the very people ondemned by the wording of the Act, it was adminis-ered in such a half-hearted way as to be practically a ead letter It was asserted, for example, that only some ix or seven analysts were appointed, of whom four ere allowed to do nothing and two others received at irst a few samples, dwindling to extinction by inertia The only analyst who insisted on his rights was Dr CAMERON of Dublin, who in 1862 examined 2600 amples of food and drugs, proved 1500 to be adulter-ated, and secured 342 convictions In the same year only 00 samples were examined in the whole of England and Wales In 1872 the provisions of the 1860 Act were extended to drugs, which were undeniably in need of he same protection as foods, and a tentative if some-what naive attempt was made to control labelling as well as actual sales Difficulties in the working of this Act and its obvious shortcomings led finally to the Act of 1875, which, although subsequently amended, extended, and supplemented many times up to 1955, is still the basis on which rests all the communal efforts in nearly all civilised countries to secure that food shall be safe Today we can only look back in wonder on the time when it was possible for a confectioner to escape with a fine of sixpence for colouring his cakes with lead chromate

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Annotations

ANTI-HISTAMINES AND PROTECTION AGAINST LIVER INJURY

THE complex mechanisms underlying the integrity of living cells can no doubt be disturbed in many ways, but the disturbance may commonly be at the same vulnerable point. Judah et al [1] [2] have drawn attention to this important possibility, and have produced strong evidence that this common vulnerable point is the mitochondrial membrane and that measures to reduce its permeability may afford protection against widely diverse injurious agents

These workers showed in 1956 [2] that the action of several liver poisons—*for example, carbon tetrachloride*—is associated with mitochondrial swelling and loss of enzymes into the suspending fluid, and further work with the liver carcinogen, thioacetamide, indicated the important damaging role of calcium ions [3] This work with thioacetamide has been restudied by Judah.[1] In liver slices he estimated the increase of mitochondrial membrane permeability by the amount of malic dehydrogenase that appeared in the supernatant fluid He has thereby confirmed the importance of the part played by calcium ions, and has obtained convincing evidence of the action of anti-histamines in inhibiting the increased permeability and the associated swelling of the mitochondria Since thioacetamide does not cause swelling of isolated mitochondria, he suggests that the mitochondrial changes observed with liver slices represent part of the final common pathway of liver-cell damage

The observations by Judah et al. have now been extended to a form of hepatic damage produced by a virus [4] Using Gledhill's murine hepatitis virus MHV$_3$, they obtained significant protection of mice by means of the anti-histamine, diphenhydramine hydrochloride Mice were infected with an L D$_{50}$ of the virus, and the treated group received a daily dose of 100 mg diphenhydramine hydrochloride per kg body-weight The survival-rates of the controls after 5, 6, and 7 days were 50, 31, and 16% respectively, while the corresponding figures for the treated animals were 79, 62, and 43% Evidence of protection was obtained also from histological study of the liver By the 3rd day after infection diffuse zonal necrosis was found in both groups of animals, but by the 5th day, whereas in the control animals these had become largely confluent and massive, in the treated animals they remained discretely zonal This was not the only evidence of the protective effect of the anti-histamine, for in the treated animals the serum level of malic dehydrogenase rose much less than in the untreated

The concentration of virus in the liver was determined on the 4th day by intraperitoneal inoculation of serial dilutions of liver suspension into other mice Substantially the same concentration of virus was found in the control animals and in those treated with diphenhydramine hydrochloride This observation is important, since it is in keeping with the hypothesis that the protection of the liver cells against necrosis was due not to any inhibitory action on the virus but to an action on the metabolism of the affected cells that protects against the effects of viral proliferation

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[3] Dawkins, M J R., Judah, J D Rees, K. R. *ibid* 1959 77 257

[4] Judah, J D, Bjotvedt, G., Vainio, T *Nature Lond* 1960, 187, 507

The lack at present of any specific treatment of viral hepatitis in man will no doubt prompt an early trial of the anti-histamines in this condition Serial study of liver-cell enzymes in the serum of patients treated in this way should prove a useful method of assessing the results quantitatively McLean's [5] observations on the protective effect of anti-histamines against some of the hepatic effects of nutritional deficiency suggest that these drugs may be especially valuable in the treatment of the severe forms of hepatitis in malnourished patients

BRUCELLOSIS IN BRITAIN

IN this country undulant fever, due to infection with *Brucella abortus*, arises from drinking infected milk or from contact with cattle, 15–20% of which were believed to be infected ten years ago [6] Some protection is afforded by vaccination [7 8], but complete prevention depends on eliminating the infection from cattle—a step which is also economically important A campaign against the disease in man and cattle was launched by W H O in 1951 [9], and some countries, including much of Scandinavia, have almost entirely rid themselves of this infection [10] In Britain the public health committee of the British Medical Association have recommended that the disease should be made notifiable [11]

Following the discovery of cases of brucellosis associated with the drinking of tuberculin-tested (T T) milk, doctors and veterinarians in the Oxford region formed a working group to study the incidence of the infection [12] So far only some of the results [13 14] of these surveys have been published Meanwhile a retrospective analysis based on hospital records over the past twenty years has revealed some interesting facts [12]

The recorded hospital incidence of undulant fever has remained fairly steady over the whole period, even though the number of people drinking unpasteurised milk must have fallen considerably Apparently a higher proportion of cases are being diagnosed correctly there is some evidence of such a trend elsewhere in England and Wales [15–17] Perhaps the most startling finding is that of the last 17 cases 7 were in children, of whom 4 were judged to have been infected from raw T T milk and 3 from raw undesignated milk, in addition, 5 adults had been infected from T T milk Many members of the public regard T T milk as “ safe ” [12 15], but this is a misapprehension, and samples from 5% of T T herds were found to give a positive biological test when injected into guineapigs

It is regrettable that a disease commonly due to infe milk is not notifiable, and that existing legislation ap ently does not enable the sale of cows yielding s infected milk to be prevented [7] Other countries h shown that prevention is feasible In the United King action is overdue

BIOPSY OF THE PROSTATE

MALIGNANT disease of the prostate seldom gives ris symptoms until the growth has extended beyond scope of radical operation In some instances, howe the chance finding of a suspicious nodule or area induration on rectal examination may lead to furt investigation before the opportunity for curative surg is lost At this stage the serum-acid-phosphatase valu unlikely to be conspicuously raised, and radiograp examination will only help to exclude secondary spre Confirmation of the diagnosis must, therefore, dep either on biopsy or on examination of expressed prost fluid for exfoliated cancer cells With this latter proced the findings are often difficult to interpret, and the res can be relied on only when an expert cytologist ma the examination For this reason biopsy may be reso to, particularly as a prelude to radical surgery or when other purposes definite proof of malignancy is need

Needle biopsy by the perineal route has proved b accurate and safe in the hands of some, including Pa and Finelli,[1] who report a series of 66 consecutive biops on suspicious prostatic nodules using the Vim-Silverm needle (or its Franklin modification) Most of the spe mens were obtained under local anæsthesia, and no co plications were recorded Suitable material for mic scopy was obtained in all but 6 The cases were segrega before biopsy into three groups according to whet cancer was regarded as strongly probable, probable, merely suspected on clinical grounds In the first gro microscopic evidence of cancer was obtained in 18 out 21 patients (86%), in the intermediate group in 10 out 24 (42%), and in the improbable group in 3 out of (20%) Thus the results of clinical assessment accord to some extent with those of biopsy evaluation, and t findings tend to support the view that in about 50% cases a suspicious prostatic nodule will prove to be least potentially malignant

Nevertheless the place of biopsy in suspected prosta cancer needs to be considered further In experienc hands diagnostic material may be secured in a high pr portion of cases without undue difficulty, but it is all t easy to obtain unrepresentative tissue at the cost to t patient of some discomfort and occasional risk Admitted the danger of disseminating the disease by “ blind ” inte ference with the neoplasm has been exaggerated—a fa underlined by the frequency with which perureth prostatic resection is carried out without promoting rap metastatic spread But the real risk of prostatic biopsy suspicious early lesions lies in the interpretation placed o a “ positive ” result As is now well known, with advan ing age isolated foci of latent cancer in the prostate becom increasingly prevalent Many of these never progress activity, and in the elderly symptom-free patient th are often best disregarded In younger patients, howeve the question of surgical treatment (as opposed to endo crine therapy) may arise, and it is in such cases that th action which should follow a positive biopsy finding least clearly agreed But it is now widely accepted tha where the diagnosis cannot definitely be established by ither means, biopsy is desirable before endocrine therapy s instituted and obligatory if radical operation is conemplated Disappointingly, in the series reported by Parry and Finelli, only 6 of the 31 patients in whom the presence of a cancerous nodule was proved were deemed suitable for an attempt at curative surgery

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[6] Dalrymple Champneys, W *Lancet*, 1950, i, 429
[7] Elberg S *in* Bacterial and Mycotic Infections of Man (edited by R J Dubos) London
[8] *Tech Rep Wld Hlth Org* 1958, no 118 See *Lancet*, 1958, ii, 273
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[12] Bothwell, P W *Med Offr*, 1960, 103, 85
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[15] Barrett, G M , Rickards, A G *Quart J Med* 1952, 22, 23
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SOYA-BEAN GOITRE IN INFANTS

In the United States, many infants who are supposedly intolerant of milk have been reared on soya-bean preparations In a few of them goitre has developed, often with indications of mild hypothyroidism as well Rawson and Rall[1] described the first example, another was studied by Van Wyk et al[2] who had heard of 8 other possible cases, and now 3 more have been recorded in detail by Shepard et al[3] The goitre disappeared rapidly in Van Wyk's case and in 2 of Shepard's cases when the diet was changed from the soya-bean preparation to milk. In the 3rd patient studied by Shepard the goitre vanished when iodide was given, but unfortunately the soya-bean preparation was also changed at the same time

McCarrison[4] first showed that soya-bean flour can cause goitre in rats, his findings have been amply confirmed[5–7] The commercial preparation actually consumed by Van Wyk's and Shepard's infants was shown in the laboratories of the manufacturer to be goitrogenic to rats[8] Goitres were preventable by iodide supplements, and these have now been incorporated in the formula Another soya-bean preparation for infant feeding, made by a different firm, is apparently not goitrogenic even when not supplemented with extra iodide[9]

The mechanism of soya-bean goitre in laboratory animals is not clear No goitrogen has so far been identified Van Middlesworth[10] has suggested that soya-bean flour (like cellulose) tends to prevent the reabsorption of thyroxine reaching the gut through the bile The amount of thyroxine a rat might lose in this way would probably be quite considerable, since the relative bulk of fæces is large in this species The loss of thyroxine would demand a compensatory increase in the activity of the thyroid, probably with an increase in the size of the gland The iodine contained in the fæcal thyroxine might or might not be lost to the rat, according to whether or not it was split off by microorganisms in the gut, and reabsorbed as iodide Hence the rat's thyroid might have to respond to an increased demand for thyroxine with a simultaneous deficit of iodine The combination would be highly goitrogenic

It is not very likely that this ingenious hypothesis applies to human soya-bean goitre, since the fæcal excretion of thyroxine is relatively unimportant in man (it seems to be related to fæcal volume, which is relatively small in the human species[11]) The mechanism of soya-bean goitre in man therefore remains unexplained, although it seems likely to be iodide-dependent The condition does not seem to have been encountered so far in this country, probably because pædiatricians here are reluctant to diagnose milk allergy and hence soya-bean diets are seldom prescribed But where such diets are prescribed the clinician should remember the possibility of a goitre developing

Probably no adults consume soya-bean products in sufficient quantity to cause goitre Van Wyk et al[2] showed that the soya-bean preparation which caused goitre in infants did not affect radioiodine uptake in adults (though in 2 out of 14 subjects the amount of labelled organic iodine appearing in the plasma was decreased) It is interesting to recall Iversen's[12] tentative suggestion that the cessation of imports of soya-bean into Denmark might have had some share in causing the remarkable epidemic of thyrotoxicosis in that country during the 1939–45 war He suggested that soya-bean products (used in the manufacture of margarine and cattle cake) might in normal times exercise a restraining influence on thyroid function This highly ingenious hypothesis seems improbable for various reasons, one of which is that the goitrogenic activity of the soya-bean is unlikely to survive the processes of manufacture, at least in the case of margarine[5 7]

IATROGENIC SODIUM RETENTION

Sodium retention is a well-known complication of treatment with some drugs The most important of these is cortisone, but in long-continued treatment cortisone has now been replaced by prednisone and dexamethasone, with which sodium retention is more unusual This complication—presenting with hypertension, pulmonary œdema, or congestive heart-failure—may also follow administration of œstrogens, particularly in old men with myocardial disease who are receiving large doses on account of carcinoma of the prostate, but it may also arise during the (doubtfully effective) treatment of coronary-artery atheroma with œstrogens[13] Phenylbutazone and reserpine are other drugs that may cause sodium and water retention

Thoughtlessly or unwittingly, medicines containing sodium may be prescribed for patients on low-salt regimes Rimer and Frankland[14] describe two cases in which fluid retention was increased owing to sodium in an antacid mixture Their analysis showed that some common antacids contain important amounts of sodium 'Aludrox', for instance, was found to contain 33 mg sodium per oz, and 'Gelusil' 5 3 mg per tablet Other common medicines, such as mist gent alk, mist kaolin et morph, and 'Eno Fruit Salt', also contain sodium And the Brompton hot water mixture (mist sod chlorid co, *N.F*), which is sometimes given to bronchitic patients in heart-failure, contains 260 mg sodium in each 1/2 oz dose

The dangers of sodium-salicylate treatment in rheumatic fever, especially if the patient is also receiving large doses of cortisone, are increasingly recognised Pulmonary œdema from this cause was described by Phear[15], and sodium salicylate should be replaced by aspirin if heart-failure develops or if there is rapid weight gain[16]

All this we may know but do not always remember as we scribble our prescriptions

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Special Articles

FIXED COSTS IN THE HEALTH SERVICE

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M.A , M D Cantab , M R.C P
LATELY GOODWIN TRAVELLING FELLOW OF ST JOHN'S COLLEGE, CAMBRIDGE, AT HARVARD GRADUATE SCHOOL OF BUSINESS ADMINISTRATION

IN earlier papers I pointed out that the percentage of national income spent on medical care in the United States and in Britain has tended to remain constant over a number of years [1] I further suggested that future expenditure on the health service in Britain could be predicted on the assumption that for the next few years this proportion is unlikely to change greatly In making this prediction I discounted possible changes in the use of the service as irrelevant

The purpose of this paper is to show that the use of the the health service does not determine its cost It will do this by considering the distinction between fixed and variable costs

COSTS IN INDUSTRY

A " fixed " cost is an expense which is incurred independently of the quantity of goods sold or produced, or the number of services rendered A " variable " cost is an expense which varies more or less directly with the volume of production The difference can be illustrated by examples drawn from industry

In *retail distribution* most costs are variable

A retailer buys refrigerators from a wholesaler or manufacturer, their total cost to him varies directly with the number sold He also has to pay rent, rates, heating, lighting, insurance, and the salaries of salesmen, secretaries, and cleaners These costs, which are often called overheads, are fixed and remain the same whether he sells one, two, three, or four refrigerators Fig 1 shows the relation of total costs to quantity of goods sold in a distributive organisation

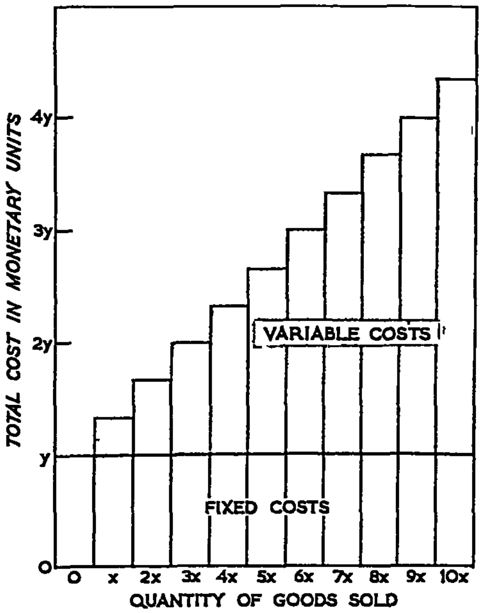

Fig 1—Cost structure of a distributive organisation.

In *manufacturing industries* also, many of the costs are variable

In a factory making refrigerators the cost of the castings and sheet-metal from which finished parts are made, and of component parts bought from other firms, varies with the number of machines produced The cost of the direct labour used, such as the machine-tool operators and the assembly-line workers, may be considered variable on the assumption that the wages for unit work remain the same whatever the volume of production This assumption is reasonable if the workers can either be hired or fired as production varies,† or can be immediately transferred to, or from, other productive work within the plant. In addition, as with retail distribution, there are also fixed costs or overheads which are largely independent of the number of refrigerators produced—that is whether the factory is producing at full or half capacity

In most *service industries*, however, nearly all costs are fixed The existence of the service, not the use of it, determines its cost

The cost of running an express train a hundred miles is about the same whether there is 1 passenger in it or 1000, the cost of flying an aeroplane across the Atlantic empty or full of passengers is much the same, the cost of a town fire-brigade in a year when there are no fires and in a year when there are several is much the same, the cost of showing a film in a cinema containing an audience of 2 or of 2000 is almost exactly the same The cost structure of a service industry is shown in fig 2

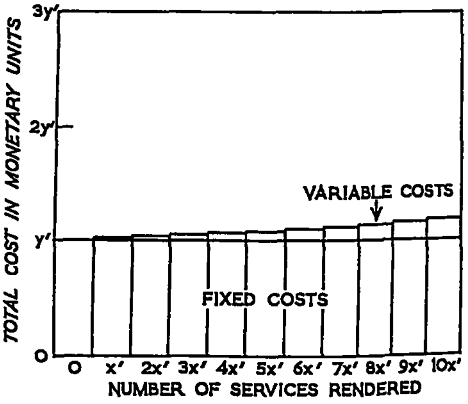

Fig 2—Cost structure of a service organisation

FIXED HEALTH SERVICE COSTS

In the health service most of the costs are fixed, and only a few are variable

The cost of the *general practitioner* service is almost entirely fixed The doctor is paid a fee per patient per year, irrespective of the number of visits made, patients seen, or time worked. Thus, if in a single month there are widespread epidemics of influenza, measles, and gastroenteritis, the doctors will work long hours and see many more patients than usual, but the total expenditure on general practitioners will remain almost constant In a fine summer month free of epidemics, the number of services rendered may fall substantially, but expenditure is little less

The expenditure on *hospitals* accounts for about 60% of all health service expenditure Over 80% of hospital current expenditure, and all capital expenditure, represent fixed costs The salaries and wages of nurses, doctors, laboratory technicians, physiotherapists, radiographers, administrators, secretaries, porters, engineers, cooks, and wardmaids, and the cost of heating, lighting, and maintenance, are the same whether the hospital is full or half-empty The cost of food, drugs, laboratory and radiographic materials, and so on represent less than 20% of the cost of running the hospitals, and these are the only costs which are reduced if a hospital is partly empty

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[1] Seale, J R *Lancet*, 1959, ii, 555 *ibid* 1960, i, 1399

† The assumption that all direct labour costs in industry are variable is less reasonable today than it was before the second world war With guaranteed minimum wages (e g , for British dock-workers and American automobile-workers) and redundancy compensation agreements (e g , for Lancashire cotton-mill operatives and Welsh coalminers), the wages paid to many industrial workers no longer fall immediately production falls Also, in a period of full employment, management often does not lay off workers as soon as demand for a product falls, lest it finds itself unable to recruit workers again when demand next rises The effect of such developments is to increase the proportion of costs which are fixed in these industries

In the *local health authority* services, costs are largely unrelated to use. The costs of the district nurses and midwives, the health visitors, the maternity and child-welfare clinics, and even the ambulance service are mostly fixed.

This description of costs in the health service is oversimplified. The use of a service can gradually alter its cost by affecting the fixed costs *If in an individual hospital the* number of patients using it falls dramatically and persistently, as has happened in fever hospitals and is happening in tuberculosis and children's hospitals in all the prosperous nations, then the number of staff employed may be decreased, thus lowering the fixed costs A ward, a wing, a whole hospital, may be closed But the closing of a ward does not necessarily decrease fixed costs It may be an opportunity to allow the hospital staff to work shorter hours or to earn more,[‡] or to give the patients in the remaining wards more care Nor does the closing of an entire hospital necessarily have any effect on the national expenditure. If the redundant employees from a closed fever hospital transfer to a new geriatric hospital, or to other hospitals to provide a better service, or to a home-care service, then total expenditure on the service may remain unaltered

Conversely, if there is persistent pressure for patients to be admitted to a hospital where the bed-occupancy rate is already nearly 100%, then a new ward or a new hospital may be built. This would lead to a large capital expenditure and increased fixed costs But this pressure, though a necessary cause, is not alone enough to bring this about Men, materials, and money must be available and the will to use them for this purpose Without them the new hospital will not materialise, and there will be no increase in fixed costs

VARIABLE HEALTH SERVICE COSTS

The costs of the *ophthalmic, dental, and pharmaceutical services* appear at first sight to be variable, because payment depends on items of service rendered or goods supplied If an optician doubles the number of spectacles he supplies, his payments are doubled, if a dentist extracts half as many teeth, his payments are halved, if a general practitioner increases the dose of prednisolone for his patient from 10 mg to 20 mg daily, expenditure on this drug is doubled These three services combined have in recent years represented barely 20% of expenditure on the health service.

But though the costs of the *ophthalmic and dental services* are indeed almost all variable at the level of the individual optician or dentist, it would be a mistake to conclude that they are 100% variable at a national level They primarily represent the incomes of dentists and opticians, and large changes in the use of the services they provide would lead to large changes in their incomes if unit payments remained constant. This happened in the early months of the health service, when the incomes of most dentists and opticians rose substantially But piece-work rates in any organisation are set not at an arbitrary level but at a level which will allow a reasonable income Thus a large rise in the number of services rendered, causing steeply rising incomes, tends to a cut in the fee paid per item of service This happened in 1949 and 1950 to the fees paid to dentists and opticians Similarly a fall in the number of services will tend to a rise in individual fees These tendencies are well illustrated by the Royal Commission's recommendation that arrangements should be made to ensure that the average annual income of dentists from health-service fees should be £2500 net

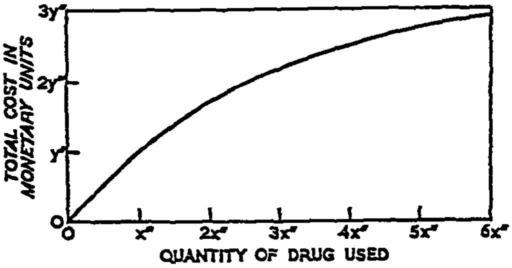

Fig 3—Cost of a drug to the National Health Service.

In the *pharmaceutical service* similar tendencies are present. When a new drug such as penicillin, streptomycin, or cortisone is introduced, unit cost is initially very high. With mass production and mass consumption expenditure would become astronomical if costs of such drugs to the health service were 100% variable But they are not, for, with quantity production, unit cost to the manufacturer falls and consequently unit price to the National Health Service also falls Thus though total expenditure on a drug rises with increasing use, it does not do so proportionately (fig 3), for in the drug industry, as in the health service, most costs are fixed

DISCUSSION

Since so many health-service costs are clearly fixed, would it not be reasonable to assume that, at a national level, virtually all costs in the National Health Service—or indeed in any form of health service—are fixed? This would imply that the cost structure of the whole service could be represented by fig 2 with the variable costs excluded Changes in the use of the service would not in practice affect significantly its total cost, and could be ignored when budgeting for the future. This is not to say that how the health service is used is irrelevant, for its use is the reason for its existence, it does say, however, that factors other than its use determine its cost To understand what these are we must look at the fixed costs

The fixed costs primarily represent the incomes of those employed, directly or indirectly, by the service If the proportion of the working population whose incomes are derived from providing medical care remains constant, and if their incomes, relative to the incomes of the rest of the nation, do not change, then the proportion of national income spent on medical care will remain constant. Observations made in many countries show that this latter proportion does in fact tend to remain constant over several years[2]

If there are factors which tend to increase the proportion of the working population providing medical care, then the proportion of national income spent on medical care will tend to rise This happens during national economic depressions when many workers in the manufacturing, building, and mining industries lose their jobs, and consequently much of their income, while those providing medical care keep their jobs It also seems to happen very gradually as real per-caput national income rises[3] This gradual and apparently automatic shift of people into occupations such as nursing, medicine, and dentistry, which occurs as a nation becomes increasingly prosperous, can of course be accelerated or retarded by social policy

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[‡] In practice this does not happen in the N.H S , because rates of pay of hospital staff are determined centrally by the Ministry of Health and not by individual hospitals. It could happen, however, in a health service where financial control was decentralised.

2. International Labour Office. Cost of Medical Care, p. 152. Geneva, 1959

Thus a consideration of the nature of fixed costs, and observation of actual expenditure by nations on medical care, both lead to the conclusion that, when predicting national expenditure on medical care, or when budgeting for expenditure on the National Health Service, changes in the use of the service can be ignored, as they do not significantly affect total cost

I wish to thank Dr N F Coghill for his helpful comments on this paper

CASUALTY SERVICES

THE report on casualty services issued by the Nuffield Provincial Hospitals Trust, which is reviewed in a leading article this week, includes the following recommendations

1 The study established that there is a need for leadership and urgent executive action on the part of hospital authorities to review, reorganise and improve the service for casualties The medical staffing of such services demands special attention, particularly the provision of adequate consultant cover and the supply, supervision and training of junior staff

2 The history of casualty services records justifiable public dissatisfaction about their adequacy and also widespread apathy on the part of hospital authorities to correct faults This has been due to the low priority of the subject in schemes of reform, and this in turn seems to arise mainly from (*a*) the poor status of casualty work, and (*b*) the imprecision of the term " casualty " Casualty departments tend to embrace a wide range of categories of cases seeking attention and treatment Because of the increasing number of accidents the most urgent need is to improve the service for those casualties requiring immediate attention and treatment—i e " urgent emergency and accident cases "

3 There is therefore a need for an immediate review of the services which hospitals seek to provide in their " casualty " departments and a classification of all hospitals to denote their facilities for the reception of " urgent accident and emergency " cases Such a review should examine relevant local issues such as the " open door " policy and all the arrangements for medical care It should also include an evaluation of the function of the casualty department as a source of special teaching material

4 From the start the horizons of the surveyors were forced well beyond those of the individual hospitals visited The study showed that if adequate staffing and facilities were to be provided it would be necessary to concentrate services The organisation for casualties should be based on well-defined catchment areas and should be planned to take account of all the services for medical care already available there Such organisation will almost certainly entail the rationalisation of present services to ensure immediate diagnosis and effective treatment for those in urgent need of it It will call for the fullest cooperation between regional boards and teaching hospitals in all regions, to ensure that there is a high standard of care available to the community, including a regional postgraduate training and research centre for emergencies and for accidents At the hospital level such rationalisation will certainly involve the closing of many casualty departments as they are at present conceived, and will require special understanding from management committees and hospitals

5 Nowadays a hospital (or indeed, the hospitals) serving an area can rarely exist in isolation in providing the kind of medical care which, to be effective, must be a continuous process Because of the recent growth and development of industrial health services there is a need for future hospital arrangements to include provision for close cooperation with such services, strengthened, perhaps, by clinical assistantships in hospitals for industrial medical officers

6 Equally, the service provided by general practitioners has a bearing on the way in which casualty departments are used by the public Because of the importance of providing a service for the relatively minor, non-urgent conditions, there is need for the fullest consultation between the hospitals and local medical committees (and other appropriate bodies) as to how general practitioners can help to relieve the hospital of the burden of such cases, and so enable the hospitals to concentrate on what they are best fitted to do The question of employing general practitioners as clinical assistants should be explored, not only because there is undoubtedly a shortage of suitable junior staff, but because such a move would strengthen the essential links between the hospital and community services

7 It is difficult to generalise about the kind of organisation required by the hospital service to meet the needs of any one region, or even community, because there is insufficient information available at present about the variation in frequency and type of casualties in the case-loads of departments Certain main principles are put forward as fundamental to the arrangements for dealing with urgent accident and emergency cases The most important is that there should be full twenty-four hour cover by doctors adequately trained for the work they are called upon to do, and who are assured of the stability and importance of this phase of their medical career The organisation needed will obviously vary from area to area and facts should be obtained about the incidence, and in particular the kind, of emergencies and accidents coming to the hospital in each area

8 It would be a mistake to assume that all the relevant facts can be easily gathered by simple statistical methods To obtain the necessary background information, regional hospital boards should, in association with teaching hospitals, consider setting up multi-interest surveying teams, properly constituted and consisting not only of practising clinicians but others with experience in the interpretation of demographic data Such teams should have secretarial help and be properly advised on statistical, sociological and administrative matters, as well as on organisation and methods They should also have wide terms of reference, to include not only the study, in all areas of a region, of the organisation for dealing with major casualties —which in any case, because of the drama attached to them, may already be relatively well provided for—but also how the run-of-the-mill material which makes up the bulk of so-called " casualty work " is at present being dealt with They should also look at this work in relation to the other services of the hospital, including rehabilitation and resettlement arrangements, and to the effect of prolonged and preventable disability on the individual and the community In view of the increasing problem of cross-infection, special regard should be paid in such surveys to the control of sepsis

9 Methods for helping the work of such surveying groups should be developed, including systems of records designed to produce relevant, up-to-date information A method of noting features of casualty departments, capable of further development as necessary, is suggested for use by such groups, and an account is given of a simple records system—specially designed for sampling—to extract the basic data needed for the study of the range and depth of the work of casualty departments

10 In view of the poor accommodation in the newer departments visited, it is strongly recommended that the functional requirements of casualty departments should be carefully studied in conjunction with all practising personnel, and the results applied in new buildings, as well as in the adaptation of existing accommodation

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[3] Seale, J R *Lancet*, 1959, ii, 555

Points of View

SPORTS MEDICINE

J. D. G. TROUP
M.R.C.S.

SPORTS medicine is not a recognised specialty in this country, yet the need for it is obvious. Medical centres, where research for sport is going forward, exist in Finland, Sweden, Russia, and West Berlin. In them investigations are made into the physiology, the psychology, and the statistics of sports medicine. It would be absurd to say that the United Kingdom lags behind in sport for lack of medical sport specialists, but it is certain that a very useful contribution towards training methods, and hence performance, could be made. But that is not all, because what can be learnt from sport has a tremendous bearing on some of the illnesses which come under the vague heading of rheumatism, and probably on others besides.

In this country medicine only provides a supervisory service for sport. It attempts to advise on the prevention of permanent damage, and to provide first-aid facilities and rehabilitation after injury. Medicine is not very clever when it comes to coping with the sprains and strains to which athletes are subject. If these lesions do not heal on their own, or after a period of rest, the athlete has to give up. There must be many hundreds of athletes and sportsmen who, because of a recurrence of symptoms whenever they begin intensive training after resting, have had to discontinue all but the gentlest activity. Very little is understood of these injuries, and their diagnostic labels are among the most meaningless in all medicine. This is partly because disappointingly little is known about the mechanics of the body, and therefore doctors are correspondingly inept at treating the disabilities which arise from mechanical strains. We know practically nothing of what renders a joint unstable, unbalanced, and hence subject to injury. Consequently we are in no better position to advise the sportsman how to avoid injury and strain than are his trainers.

* * *

This is important to Medicine because the minor injuries and strains to which the athlete is subject are closely related to some similar conditions which are classified as rheumatism, fibrositis, lumbago, "neuritis", and so on. These conditions take up more of the profession's time than practically any other single group of diseases, and they all have one thing in common—they represent deviations from the normal mechanical efficiency of the body. The symptoms of which the athlete complains can be easily cured if he gives up athletics, but the same thing in the tired middle-aged housewife has to be palliated and endured.

Thus the more we can learn from the disabilities and difficulties experienced by athletes, the more we are likely to help the tired middle-aged housewife to be less tired and to forget that she is middle-aged. One of the most unfortunate things a doctor can say to a patient is "Well, you are not as young as you were, and you have to expect some aches and pains. After all your joints don't last for ever, it's just fair wear and tear." This reassuring information, coupled with advice to take it easy and to rest, is only practical if the patient had been entertaining fears of malignant disease. Otherwise it means that the doctor does not know how to help.

This may seem unfair to those who, in all good faith, have found no way of relieving a patient's symptoms, and who are confronted by palpable evidence of degenerative processes. Osteoarthritis has got to begin somehow. Though essentially a degenerative process it must be preceded by such factors as loss of function, local circulatory failure, or neurodystrophic processes, or by a combination of all three. If the history is taken carefully and exhaustively, almost invariably one finds that the process began with a minor injury, an attack of lumbago, or some other sprain type of lesion—the sort of lesion which can be the result of a minor injury or some repeated strain, and of which healing was incomplete. A man may sprain an ankle, though not badly enough to seek medical advice, and after the first flush of inflammation has subsided, he remains symptom-free provided he does not exert himself. Many people never do exert themselves, and such people commonly adopt unconsciously some postural deviation, which relieves the strain from the unhealed lesion but which imposes a mild chronic strain elsewhere. Furthermore, one-sided muscle weakness is bound to follow the loss of function and the adoption of a postural fault. Degenerative processes could well begin like this, and they do, loss of function being the key ætiological factor.

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The average young man of sedentary habit, if otherwise healthy, can easily cover a mile in 10 minutes if pushed to it. After a week's training he can probably do it in 6 or 7 minutes, and in a month or so, if driven, in 5 or 6 minutes. But if he wants to run a mile in 4 minutes, he must train intensively for a long time; he would probably have had to begin in his 'teens, gradually improving his performance as he gained experience of competitive athletics.

In rather the same way a patient with a disability, such as an osteoarthritic hip, has to go into training if he wishes to overcome the disability and live a normal life. The onset of osteoarthritis in the hip commonly dates back to an injury causing low-back pain and pain and weakness in the leg—an injury which probably caused a sacroiliac lesion or strain. The patient clearly never recovered full function after the injury, and the stiffness of the hip and associated pain developed from that time. In practice, even when the osteoarthritis is advanced, it is worth trying to relieve the loss of function which set off the osteoarthritic processes. An arthritic can gain remarkable relief and improvement if he is prepared to "go into training". The trouble is that, once the disability is there, he has to keep in training.

A mass of information is already available on how to increase the strength, bulk, and endurance of muscles, and on related factors such as reaction-time and speed of contraction. But what we want to know is something about the strength of muscles or muscle groups which act on a joint, and their relation to injury of that joint, the suppleness of the joint, and all the interrelated factors affecting joints under stress. If "sports medicine" can answer these questions, we shall learn a great deal about treating sports injuries, about athletic training methods, physical education, the prevention of joint degeneration, and about the treatment of the common skeletal aches and pains.

In a report[1] in which the contribution of sports to medicine is discussed, the World Health Organisation refers rather vaguely to "functional disturbances of autonomous regulation (which) . form a considerable proportion of the clientele of practising physicians (and for which) evidence suggests that physical exercise, suitably in the form of sport, is a valuable means for the prevention and treatment of such disturbances " This is a beginning, though, as contributions to the subject go, not a very stimulating one

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[1] World Health Organisation (1959). Preliminary Report on Sports Medicine (reprinted in the Physical Education Yearbook 1959-60).

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The advance of civilisation is changing our way of life at a speed which is gathering momentum The process began with the growth of domestic architecture and the installation of furniture, and has sped along with the help of the easy chair It began with the introduction of the horse as a means of transport, and is accelerating as buses, motorcars, trains, mechanical handling, and automation take hold But the evolution of Man has gone on over a length of time which makes the few centuries of civilisation seem but a moment, and it will take us tens of thousands of years to evolve into an animal which is adapted to this life of cushioned idleness We cannot wait that long The sooner we get down to it, and learn the extent to which our wellbeing depends on the mechanical and functional efficiency of the body, the better " Sports medicine " is more likely than anything else to provide the answers.

Public Health

ACUTE COPPER POISONING

An Outbreak Traced to Contaminated Water from a Corroded Geyser

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DURING the past eighteen years, the number of cases of food poisoning from all causes has risen from 119 in 1941 to 7300 in 1958 Although the majority of these were attributed to salmonellæ, many (21,501) causes remained unidentified, and only 27 during that period were attributed to chemicals

We have recently investigated an outbreak of 18 cases of acute gastroenteritis traced to copper contamination of water from a canteen geyser The mode of this contamination leads us to believe that this form of poisoning may be more common than is supposed

THE OUTBREAK

On June 10, 18 of 150 workers in a Liverpool factory collapsed with moderate to severe gastroenteritis after drinking tea in the factory canteen Their symptoms, consisting of severe abdominal pain with vomiting and diarrhœa, headache, and dizziness, which occurred either immediately or within five to ten minutes of drinking tea, suggested an acute chemical poisoning

2 of the victims were so collapsed that they were admitted to hospital for twenty-four to thirty-six hours Chemical analysis of their fæces showed the presence of copper in concentrations of 80 and 50 parts per million (p p m) A diagnosis of copper poisoning was mac Over the next four weeks, regular chemical analysis their fæces showed decreasing quantities of copper, co firming the diagnosis of acute rather than chronic copp poisoning

SOURCE OF COPPER POISONING

The tea was prepared in large aluminium teapots, ea holding sufficient tea for 18 cups, the water was boiled a gas-heated geyser All 18 victims had drunk tea from t same teapot, this being the last pot of tea made th morning Unfortunately, the residue of the teapot h been discarded, but the geyser which supplied the wat was tested 3 pints of water were drawn off and macr scopically this sample showed a brownish tinge due suspended particles of matter with a similarly-colour sediment Chemical analysis showed that this was due suspended particles of copper sulphate The water w very slightly acid (pH 6 7) and the total copper suspension was 44 p p m

The geyser was now dismantled and examined consisted of a gas-heated all-purpose water boil holding 10 gallons Externally it was chromium-plate but the inside part of the boiler and lid was made copper Examination of the internal parts showed blue-grey deposit of copper sulphate encrusted over t top of the boiler lid and around the opening for the flo control arm The boiler was cleaned and re-assemble The result of chemical analysis of water from the geys after cleaning was negative for copper

DISCUSSION

We can trace only three recent references to illne attributable to copper contamination of water fro geysers

Griffin [1] reported an outbreak in which drinking water h become contaminated from a corroded geyser Copper drinking water was responsible for an earlier outbreak whe the water had been boiled in a large untinned and unlin copper [2] More recently, in 1956, 5 cases of acute copp poisoning occurred in a factory canteen and this outbreak w apparently due to copper salts from a gas geyser, which ha contaminated water stored in it overnight and used to make t the following day In this outbreak it was established th copper salts from the flue could have fallen into the water Th water used for the tea was not available for examination, bu a further sample yielded 10 p p m of copper [3]

In this Liverpool outbreak, drinking water was agai contaminated by copper salts from a corroded geyser, an it is interesting to examine the reason why only 18 person were affected out of the 150 who were at risk

For the purpose of tea making, there were six $4^1/_2$ pin aluminium teapots in use and tea was prepared by puttin a $1^1/_2$ oz packet of tea in each teapot and adding boilin water from the geyser as required When the geyser wa dismantled for examination, a heavy deposit of coppe sulphate was found on the upper and inner cover of th copper boiler To one side of this cover there was circular hole (2 in in diameter) to give access to the arm of the float Close to this hole there was a bare patch from which it was concluded that a portion of the coppe sulphate had recently broken off This chemical deposi may have been dislodged from the lid by some sudden disturbance such as the jarring of the teapot against th boiler outlet-tap, so causing the copper sulphate to fal through the hole into the boiling water, and, the tap being

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1 Griffin, A J B *J R sanit Inst* 1951, 71, 1
2 Hebblethwaite, A S *Publ Hlth,* 1928, 41, 276
3 *Mon Bull Minist Hlth Lab Serv* 1957, 16, 211

open, the current of flow may have enabled the chemical to pass from the boiler through the tap into the teapot If this is the correct explanation of the presence of copper in the teapot, it would account for there being only 18 victims out of 150 who were served with canteen tea on that particular morning

The geyser in this canteen was of a type that is in common use The makers state in their maintenance manual that in hard-water districts the interior surface of the boiler would require cleaning every three to four months to remove the scale deposited In soft-water districts, they state, there is rarely any necessity for internal cleaning, servicing, when required, is reduced to the cleaning of burner and flue-ways, renewal of all valve washers, regreasing of gas cocks, and to adjusting the automatic gas-valve No mention is made specifically of the formation of copper-sulphate deposits Inquiry showed that this particular geyser had never been dismantled for cleaning or scaling, and it had been in constant use since 1949

SUMMARY AND CONCLUSIONS

An outbreak of 18 cases of gastroenteritis occurred in a Liverpool factory canteen owing to the contamination of tea by copper from a corroded geyser

We recommend that this type of geyser should carry a revised maintenance instruction booklet, indicating the possibility of the formation of copper-sulphate deposits and the methods by which these deposits can safely be removed This form of maintenance should be carried out every three to six months

We wish to thank Mr J F Clark, Analyst for the City of Liverpool, for the chemical analysis of the tea water and the fæcal specimens

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Food Hygiene

New Food Hygiene (General) Regulations,[1] made jointly by the Minister of Health and the Minister of Agriculture, Fisheries, and Food, consolidate the Food Hygiene Regulations 1955–57, with some small amendments, which include (1) the application of the regulations to the handling and service of food on board certain ships and vessels, and (2) the relaxation of some of the requirements relating to temperature at which certain foods must be kept in catering premises The regulations come into force on Oct 1

In the new Food Hygiene (Docks, Carriers, &c.) Regulations[2] the most important differences from the Food Hygiene (General) Regulations include the following (1) a distinction is made between the obligations of persons allocating accommodation for handling food and those of employers who occupy the accommodation for handling food, (2) the obligations of dockers and porters as to cleanliness, clothing, &c, are limited to occasions when they are handling food which is not packed in such a way as to prevent the food from coming into contact with any surface that the package may touch, (3) certain requirements relating to structure and washing and sanitary facilities are less stringent, and (4) the primary obligations with regard to structural requirements at premises have been placed on the owner The regulations come into force on Nov 1, except for some which may involve alterations to premises or equipment. These are deferred until May 1, 1961

Certification of Stillbirths

In England and Wales from Oct. 1, doctors and midwives certifying stillbirths will be required to state the cause of death.[3] This is already required in Scotland

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[1] S.I 1960, no. 1601
[2] S.I 1960, no 1602
[3] S.I. 1960, nos. 1603, 1604

Conferences

NUTRITION

THE fact that President EISENHOWER took the trouble to attend the opening session of the Fifth International Congress on Nutrition, held in Washington from Sept 1 to 7—and made a cogent speech in which he pointed out that transferring food from one country to another as a gift might seem to the recipient to be a good and altruistic act, yet at the same time it could ruin the economy of a third equally deserving country—underlines the importance to the world today of food and the science of nutrition

The congress also showed that large international meetings can be organised without their purpose being swamped in the sheer traffic of the numbers attending At Washington there were between two thousand and three thousand people from sixty-odd countries The meetings were primarily arranged as a series of panel discussions of previously printed communications, but all this led up to a full day's plenary session to consider the world's food needs and the food resources available to meet them This was opened by the U S SECRETARY OF AGRICULTURE, who came, as Mr Eisenhower had come six days before, to emphasise again how much depended on the wise application and development of scientific knowledge

Prof JAMES BONNER (California Institute of Technology) said that, if the present rate of growth continues unchecked, the world's present population of 2900 million will be doubled in the year 2000, and, if we do not check it by conscious design, the present rate of breeding must stop at any rate by A.D 2660, because by then the entire land area of the globe will be covered by people standing shoulder to shoulder When the epidemic of science and technology strikes a nearly stable population, the death-rate plummets and numbers shoot up until the birth-rate falls too In Japan, the lag between these events was 90 years If this time-scale is applied to the whole world today, an almost stable population of 15,000 million can be expected in 90 years If the world's population could be checked at under 10,000 million, it could be fed

Protein

The new maturity in nutrition—the welding together of the analytical and the humane—was well exemplified in the panel discussing protein Dr N S SCRIMSHAW and Dr R BRESSANI, of the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala City, described work on protein undernutrition—so-called kwashiorkor—in children. It was idle for the Victorian physician to recommend a poverty-stricken mother to take her ailing child to Egypt for the winter, it is equally unrealistic today to advise poor Central American children to drink a pint of milk a day Instead, the INCAP workers, after considering the specific aminoacid deficiencies of the diet on the one hand and the available supplies of local protein foods on the other, have devised a mixture of ground maize, sorghum, cottonseed flour, and dried yeast, suitably enriched with vitamin A and calcium, which is being successfully marketed in Guatemala and elsewhere and eagerly eaten as the sort of gruel to which people are accustomed. The therapeutic effect on malnourished children with kwashiorkor is as good as that produced by milk.

In the panel specifically discussing maternal and infant feeding, Dr PAUL GYORGY compared the nutritional value for infants of human milk on the one hand and cow's milk and a number of other substitutes on the other, and Prof

R F A **Dean** (Uganda) discussed further aspects of the problem of protein malnutrition

Prof D B **Jelliffe** and Dr F J **Bennett** (Uganda) emphasised once more that the science of nutrition, when it is applied to the practical problems of human life, human behaviour, and human disease, cannot be treated as a science apart if it is to be effective Besides understanding biochemistry and physiology, the public-health nutritionist must know about the culture patterns of the people with whom he is dealing and must operate within the framework of their ideas, attitudes, and beliefs The nutritionist faced with a case of kwashiorkor knows that the sick child, by being sent to stay with relatives, is being deprived of protein, but he is a better public-health worker if he is also aware that by leaving home the child may be gaining his inheritance, and a good education as well.

Processing and Additives

Food technology exerts a very direct effect on nutrition, whether the diet is made up of the sort of foods to which we are accustomed in wealthy and sophisticated cities or whether it comprises cottonseed flour for village children in Central America It was understandable, therefore, to find a panel discussing the effects of processing and additives on food

This discussion was opened by Dr S K **Kon** (Reading), who talked about cow's milk and deplored the atmosphere of sanctity which had hung about it and frustrated even such simple and desirable technological acts as pasteurisation Now that it can be more clearly seen that people in the rich section of the world may actively harm themselves with creamy milk, while those of the poor majority in other parts must protect themselves against the hazards of infection, there is force in Kon's prophecy that the future for liquid milk is to be dried

Nowadays, the impossible task of proving the negative proposition that something added to food is harmless is taken as proved when it is shown that animals suffer no harm when fed, not twice, or sixteen times, or even sixty times, but the tidy factor of one hundred times the amount of the material in question that people could reasonably expect to eat This axiom is now hallowed by the approval of an F A.O /W H O Expert Committee Clearly, food technologists must take precautions to ensure that the foods they produce are safe, but, as Dr B L **Oser** (New York) pointed out, a balance must be maintained, and harmless, nutritious, but uneaten food contributes less to nutrition than the same article presented more colourfully and less decayed and consequently eaten

Domestic Animals

The nutrition of domestic animals has a double interest study of their own physiological needs advances the science of nutrition, and their husbandry contributes to the supplies of human food. At the Washington meeting both these aspects were reviewed.

Prof E J **Bigwood** considered the often paradoxical situation in which in some parts of the world the population of farm animals, which should support the inhabitants of the area, may in fact be in competition with the human population If animals are raised as part of the food-supply, it is obviously important that they be raised efficiently

Mr E J **Underwood** (Western Australia) considered the implications of the fact that over large areas of the Earth's surface nutritional disabilities affecting the productivity of grazing stock are now known to occur Doctors have sometimes found themselves envying their veterinary colleagues, despite the fact that animals cannot recount their own symptoms It is, therefore, worth noting Underwood's conclusion that in animals, as in man, naturally occurring nutritional deficiencies seldom exist in simple or uncomplicated form

Ischæmic Heart-disease

While most of the panel discussions were concerned with various aspects of the clamant needs of the underfed majority of the world's population—a majority which only strenuous efforts will prevent from increasing as the population doubles in the remaining 40 years of the century—one was set aside for discussing the most striking nutritional problem of the surfeited minority, among whom we British are numbered This is the sharply rising death-rate of men from middle-age onwards from ischæmic heart-disease

The case was fairly put by Dr E **Bronte-Stewart** (Cape Town) If it is accepted that ischæmic heart-disease results from atherosclerosis—and this has yet to be proved—there is evidence from epidemiological studies to suggest that a disordered lipid metabolism is in the background, and that this disorder can be accounted for by a dietary fatty-acid imbalance. Although alterations in the serum-lipids can be induced by changes in the dietary fat intake, it has yet to be shown whether or not such alterations have any bearing on the disease Nevertheless, the dietary fat hypothesis remains a good working hypothesis, because, of all the environmental variables that constitute our present-day mode of life, no other at present known can be so closely related to the pathological, metabolic, and epidemiological features of the disease

Germ-free Animals

While the panel discussions were dealing with the urgent practical problems of today's crowded Earth, never less than five simultaneous sessions were in progress at which an immense variety of 10-minute research papers were read As remarkable as any were some of those presented during the two full sessions devoted to studies of germ-free animals

The devising of the technique by which an operator, dressed in a sterilised rubber diving-suit, delivers a lamb by cæsarean section, and, after sterilising the animal, posts it through an air-lock into the sterile compartment in which it is to live, must command the respect of other investigators At the University of Notre Dame, a germ-free lamb was successfully reared for 60 days but gradually failed during the next 60—demonstrating that there is much in nutritional science still to be discovered

Magnus Pyke

ORTHOPÆDICS

The eighth congress of the Societe Internationale de Chirurgie Orthopedique et de Traumatologie was held in New York on Sept 4–9, under the presidency of Prof J **Trueta** (Oxford)

Congenital Dysplasia of the Hip

Prof **Bryan McFarland** (Liverpool) said that in assessing treatment it was necessary to have certain criteria as to the degree of dysplasia, the age of the patient, and the grade of result He had laid down three types—the mildest dysplasia, moderate displacement, and frank dislocation. He defined five grades of results—I, perfect, II, good, III, some mild persisting dysplasia, IV, subluxation, V, complete redislocation. He believed that dysplasia was not confined to the bones but extended to the soft tissues, and it was this which often caused poor results and late arthrosis Treatment should be as early as possible Manipulative reduction must be gentle without anæsthetic, and, if this was impossible, open reduction was carried out

Dr **Ivar Alvik** (Norway) reported his findings in 945 typical dysplasia hips treated under the age of 7 years 67°, were bilateral 736 hips were reduced by closed manual reduction, which was easily performed but had a high frequency of redislocation and osteochondritis Interposition of soft tissue was due to capsule or limbus, but he had never seen the limbus inverted in a hip previously untreated. Open reduction was done in 206 hips, but in only 71 as a primary procedure. He now advocated gradual reduction by traction, and open reduction only when this failed Immobilisation in the "frog position" had now been abandoned and a more moderate position with some internal rotation was used. Early weight-bearing was responsible for osteochondritis and deficiency of the acetabular roof, weight-bearing should be delayed for two years, sometimes longer, until the os acetabuli was well developed. Excessive anteversion, if present, should be corrected by osteotomy

Dr Oscar Scaglietti (Italy) discussed the place of open reduction of the dislocated hip Closed reduction was unwise in children aged 4–5 years, or if the degree of dislocation was severe, if closed reduction failed, open reduction was necessary The exposure should be ample and should be on the Smith-Petersen approach. Muscles which were tight should be discarded and the psoas tendon, which was the commonest cause of obstruction, should be lengthened. Good results were obtained in 68% after five years' follow-up The best results were obtained between the ages of 1 and 3 years and if the hip had not been previously treated.

Prof Marino Ortolani (Italy) discussed early diagnosis and the pathological changes to be found in the fœtus and at the time of birth. His findings were based on postmortem dissection of 50 pelves of fœtuses or newborn children, some premature. He said that dysplasia was always bilateral, though on one side it might regress and subsequently be unrecognised. Frank unilateral dislocation might occur during intrauterine life and was no greater in those with associated deformities than in those without them. The dual formation was due to a primary constitutional hereditary factor and a secondary environmental factor which was essentially mechanical. This might act during intrauterine life or shortly after birth Diagnosis by clinical methods was to be preferred to radiology, which was unreliable. The most reliable clinical signs were a positive "click test" and the finding of limited abduction. As a result of laxity of the capsule the limbus was progressively flattened and a secondary acetabulum might be formed.

Dr Paul C. Colonna (U S.A.) said that in young children abduction treatment, started early, was often successful, but as the child began weight-bearing the results became progressively worse. The debatable age for treatment was 3–8 years, when changes in the acetabulum and capsule were established. If the acetabulum was severely flattened and shallow, he advocated a capsular arthroplasty First, relaxation of contracted tissue was obtained by manipulation, subcutaneous tenotomy of the abductors, and skeletal traction until the femoral head was opposite the acetabulum. At operation, the acetabulum was deepened by being scooped out, and the capsule of the joint, which had been carefully preserved, was stitched over the femoral head and the head reduced into the enlarged socket. If anteversion was excessive, this was corrected by a supracondylar osteotomy five weeks later A plaster cylinder from groin to ankle was applied so that active hip movements could be started. Careful postoperative care to restore function was essential.

Dr Knud Jansen and Dr E. H. J Lorsen (Denmark) said that they had used arthrography routinely to assess the effect of treatment. 2 ml. of contrast medium was injected under anæsthesia. If the limbus was seen to be inverted this might indicate incomplete reduction and a poor final result, but Severin had shown that even in these circumstances a good result could be obtained. Repeated arthrograms would show the adaptation of the limbus There was some evidence that osteochondritis might follow injection of contrast medium. In such cases the ligamentum teres might have been damaged accidentally

Dr G Hauberg (Germany) described the results of 330 early acetabular-roof arthroplasties in which a wedge of bone was introduced just above the acetabulum. He showed that the effect of this wedge was not purely mechanical but that it actually stimulated growth of the roof

Dr W Mohing (Germany) said that a valgus position of the femoral neck resulted in deterioration of the hip-joint. There was always a tendency for valgus to increase, and if this was beyond 130 a varus osteotomy would be done. It might be necessary to repeat it later if recurrence took place. Rotation osteotomy would often be accompanied by varus.

Mr F C. Dwyer (Liverpool) said that osteochondritis of the femoral head was a not uncommon complication of the treatment of congenital dislocation of the hip If weight-bearing allowed the deformity, aggravated and severe flattening of the head was noted. He advocated the use of a patten-ended calliper for two years, and longer if necessary

Mr E. W Somerville (Oxford) emphasised the importance of finding the basic primary factor which led to dislocation of the hip and dissociating from it the secondary deformities which developed later An arthrogram would show that in a subluxation the acetabular roof was not sloping or defective, and it could be shown that the deformity of the acetabulum in dislocation was secondary as was the anteversion of the femoral neck. Laxity of the capsule resulting from prenatal parental hormonal influences was the likely cause of the instability In these circumstances there was a strong case for not allowing extension of the hips of all infants, under any circumstances, from the moment of birth for some weeks

Prof Ishihara Miki (Japan) said that the early diagnosis of congenital dislocation of the hip was very difficult. He did not believe that the click sign or any other sign was infallible. He described cases in which apparently normal hips subsequently became dislocated and where abnormal hips underwent spontaneous healing The only way of being certain regarding stability of the hips was to take X-rays with the hips in such a position that any instability would be exaggerated.

Dr Sophus von Rosen (Sweden) said that examination of children at birth between 1952 and 1960 had disclosed 39 cases of congenital dislocation of the hip Treatment was by splintage in abduction continuously for two to three months Laxity of the joint capsule was the probable cause of dislocation, and his colleague Dr Lars Andren had found that in children with dislocated hips there was an associated laxity of the pelvic ligaments generally which could be demonstrated radiologically This might be associated with the relaxing parental hormones which developed before birth.

Dr Robert D Salter (Canada) considered that in all cases of unstable congenital dislocation or sublaxation of the hip the acetabulum was defective because it was, as a whole, facing the wrong way He described an operation in which, after open reduction of the head into the acetabulum, the pelvis was osteotomised immediately above the acetabulum by means of a Gigli saw passed through the sciatic notch. The gap was widened anteriorly, and a bone graft taken from the region of the anterior superior spine was wedged in it to keep it open. The position was stabilised by the introduction of a Kirschner wire and the hip immobilised in plaster for six weeks. The longest follow-up was two and a half years, and to date the results had been very good. It was interesting that the anteversion angle did not need correction after the hip had been stabilised.

Dr Paul A. Pemberton (U S.A.) described an operation for rapid and certain correction of the instability of a dislocated hip He carried out a partial osteotomy of the pelvis above the acetabulum, levering the lower fragment down over the femoral head and keeping it in position by wedging in a bone graft. He had found that the operation gave better results in a short period of time and with fewer complications than other methods.

Dr William S Smith (U S.A.) described observations on dogs in which dislocation of the hips was produced. Typical dysplasia followed these artificial dislocations whether the dislocation resulted from open operation or closed stretching of the capsule. If, after dislocation, some foreign object was put into the acetabulum in place of the femoral head, dysplasia did not develop These findings suggested that dysplasia resulted from the absence of the femoral head from the acetabulum and was not therefore primary.

Dr. Beckett Howarth (U S.A.) said that subluxation and dislocation of the hip was prevented by a strong intact capsule. Elongation of the capsule, perhaps of hormonal origin, was the primary factor leading to displacement. First, the head was displaced laterally and later upwards. The capsule might be stretched in vitro The displacement might increase after birth. Other changes found in the acetabulum and femur were secondary

Osteogenesis in Relation to Delayed Union and Pseudarthrosis

Dr Harold B Boyd (U S A) said that bone was a specialised form of connective tissue, which accounted for its ability to join by formation of new bone Whereas other tissues all joined by fibrous tissue, the mechanism of bony union was at molecular level and was not yet understood He reported 1013 bone grafts in 842 patients with 94% ultimate success, though in 64 patients the operation had to be repeated As would be expected, pseudarthrosis was uncommon in the young, but when it occurred it should be regarded much as a congenital pseudarthrosis In the results the highest rate of success was obtained by means of intramedullary nail and bone graft and the lowest by a plate and bone graft, but there was not as much difference between the methods as might be expected The cause of failure in the tibia and forearm was usually infection, and in the humerus and femur fracture of the graft For union to occur, osteogenesis was essential This was promoted by contact, fixation, and compression It was further greatly helped by cancellous bone packed around the fracture Both experimentally and therapeutically, autogenous grafts were better than homogenous and should always be used unless there was some contraindication

Dr R Judet (France) said that bone healed like any other connective tissue Healing occurred in four stages (1) initial resting stage, (2) proliferative hypervascular stage, (3) recessive hypovascular stage, and (4) stage of consolidation and cicatrisation Non-union occurred if any of these stages did not develop If the vascular hyperplasia failed an avascular type of non-union developed, whereas if this stage persisted too long the connective tissue failed to mature and a hypervascular pseudarthrosis developed As the vascular reaction subsided the mineral-salt content of the connective tissue increased Environment played a big part in this sequence of events, which could easily be hindered by vascular damage, infection, or the introduction of foreign materials

Dr J Judet (France) described a method of treating pseudarthrosis by compression, which he said released from the connective tissue between the bone-ends certain substances which promoted union It was necessary therefore that this connective tissue should in no way be damaged No plaster fixation was necessary and sepsis was not a contraindication If necessary, the compression could be combined with a graft Union occurred in uncomplicated cases in four months and in septic cases in six months

Prof Robert D Ray (U S A) said that individual reaction to trauma varied greatly, but generally speaking, provided the trauma was within reasonable limits, cell proliferation was stimulated This reaction to trauma had been used clinically in many ways Intermittent compression acted as a stimulus, but the effect of continuous compression was still unknown Evidence supported the view that when bone was transplanted a certain number of cells survived, though this depended on the type of graft used High-speed dehydration reduced this variability Dead-bone transplants afforded immobilisation, acted as a barrier to scar tissue, and formed a matrix on which new bone could form There was some evidence that this last function was facilitated by decalcification of the graft

Discussing non-union of long bones, Prof Merle d'Aubigné (France) reported his findings in 820 patients In 94% union was ultimately obtained, though not always by the first operation The use of a bone graft combined with intramedullary nail fixation was the best method in the humerus and femur because no plaster cast was required It was less good in the forearm and tibia The essentials for union were good bone contact and long-continued and complete immobilisation

Dr J D Ramadier (France) described an operation in which pseudarthrosis of the tibia could be repaired even if some sepsis was still present This consisted in a tibiofibular synostosis performed at the fracture site, the graft being applied to the front of the fibula and the back of the tibia 30 such operations had been done

Two contributions described methods of storing bone fo long periods Both agreed that deep-freezing was the bes method but that some other method was often more practica Professor Guntz (Germany) described the use of 'Cialit solution in the preservation of bone grafts The grafts wer removed aseptically and all soft tissue was removed The were placed in the solution and were ready for use three week later To date they had remained sterile for three years Experimentally these grafts were a little slow to incorporat for two to three weeks but in the end were as fast as any othe homogenous bone They had been used in 800 operations

Professor Idelberg (Germany) described another method o bone preservation In this the grafts were placed in specia cases and immersed in 'Polacos' preserver of the consistenc of a paste This set hard with the graft in the centre of th block, which could easily be stored at room temperature Th grafts when used were almost as good as deep-freeze bone

Mr R G Taylor (Oxford) reported 72 bone-grafting operations in 68 patients with malposition and non-union of fractures of long bones These were taken from a total of 16,700 fractures treated between 1950 and 1955 at Oxford The commonest bone was the tibia, secondly, the radius, and thirdly, the femur He advocated the use of the sliding graft whenever possible If a further portion of graft was available, it should be laid alongside the fracture, and any gaps were filled with cancellous bone If alignment was satisfactory, the fibrous union was not disturbed Bony union was obtained in 97% The failures were both due to sepsis

Professor Trueta said that in general he supported the views of Judet and Judet, but had himself found little evidence to support the idea of "hypervascular" non-union Vascular penetration of the bone from the surrounding periosteum was the deciding factor, and the vascular wall took a most active part in producing new bone beyond the preliminary state of calcified cartilage The nutrient artery was always ruptured in a fracture and became thrombosed The periosteum was raised from the bone so that the ends of the bone died Cartilage cells developed on the ends of the bone and were invaded by blood-vessels That union should take place depended on the ability of these vessels to invade the cartilage and dead bone

Professor Otolengi (Argentine) said that the Phemister graft was well recognised as a means of bone grafting Chutro had in fact described this type of grafting many years ago, and he felt it should be renamed the "Chutro-Phemister" graft. The principles were (1) an autogenous cortical graft was taken with a chisel and (2) placed across the fracture subperiosteally, (3) fibrous union was not disturbed, (4) there was no metallic fixation, and (5) immobilisation must continue until consolidation

Dr G W N Eggers (U S A) said that the healing of fractures was obtained by complete metaplasia of the anaplastic fibroblast This was affected by certain physiological factors and was undoubtedly stimulated by compression. He described an experiment which clearly demonstrated this The best force of compression was that resulting from voluntary-muscle tone which should be utilised whichever method of immobilisation was employed Care must be taken that any form of internal fixation did not interfere with this factor of compression

Dr Edward L Compere (U S A) said that substances taken by mouth or injected locally into the fracture would not help bony union The most important factor in obtaining bony union was the preservation of the blood-clot Open operation should never be done unless there was some strong indication for this Rigid immobilisation was not necessary for union, and any rigid internal fixation which prevented continuous compression might cause delay If compression was too powerful it would cause bone absorption and delayed union, and the ideal degree was that provided by the tonic contracture of muscles Early weight-bearing was a further stimulus If a fracture had to be opened it was logical to try to promote union by removing chip and sliver grafts from the adjacent bone and laying them across the fracture

In England Now

A Running Commentary by Peripatetic Correspondents

OLD Doctor Tom must have had a way with him. Like getting blood out of a stone it was to run a private practice in his day Or so he used to say All very well to get paid with a pound of butter or a couple of dozen eggs, and maybe a pig at Christmas perhaps no income-tax on the perks, but hard at first to replenish his little stock of drugs, let alone pay off the mortgage on the house He solved that one by engaging a housekeeper who had a sister in the next village with a thriving general store So pills turned into butter, and butter into hillings, and shillings to pills once more in the best Economics radition I do not suppose that he would ever have paid off the mortgage on such slender margins of profit if his only other rival in the valley had not come to an untimely end at the cross-oads by the Post Office. The acceleration of a pony and trap had failed miserably to compete with one of those new horseess carriages Doctor Tom put on a black tie and took over he gentry from the vacant practice The guineas must have olled in after that. The house was his, all spick and span, with a new double garage later on where the stables used to be Bessie no longer slipped out of the back door with the butter and eggs they were needed for the servants downstairs And when the time came they laid him out on the waiting-room couch, in his best frock coat and his silk cravat The countryfolk filed past to stack their wreaths around the walls Doctor Tom must have known it was market day Peeping between the chrysanthemums and the dahlias were some unmistakable pieces of farm-cured ham, a couple of dozen eggs, and an outsize slab cake. No wonder he looked so serene he was going out where he came in.

* * *

Our New York taxi-driver described, to our great interest, his forthcoming lunch, which would consist of ham and eggs "But," he exclaimed with great emphasis, "I only eat three eggs a week as eggs contain cholesterol and cholesterol causes atherosclerosis" "Is this general in the United States?" we asked. "Oh, yes," he replied, "particularly if there has been any history of heart disorder in the family I don't eat any animal fats and have only margarine, not butter, but three eggs a week are quite safe as the newspapers have told us so"

Perhaps that is why eggs are only half a crown a dozen in the United States

* * *

As I have encroached already on the money I hope to get when our rise comes through, it seemed time to economise—but on what? Smoking, clothes, or entertainment? No, being rather overweight the obvious thing was food I suppose I must have mentioned casually to my friends about living on eggs and baked beans and spaghetti on account of my perilous financial state.

Last week a porter sidled up to me "I've left a parcel in your office, doctor" Trying not to show my excitement, I went upstairs There was an enormous newspaper parcel, inside, a lettuce I was thrilled—a free supper That night I ate the whole lettuce and a hard-boiled egg, it was satisfying, but dull, as there was nothing to go with the lettuce. The following day, the occupational therapist knocked on the door "I'm going on holiday, and heard you liked lettuce It seems a shame to waste these." In her outstretched hands was an even bigger newspaper parcel—two lettuces nestling inside On my way home I stopped at a shop and bought a small bottle of mayonnaise. For two nights I had lettuce and mayonnaise. By the fourth day I was longing for spaghetti again, but lettuces continued to arrive. The word had gone round the whole hospital by now "The doctor loves lettuce."

In the last few days I have bought ham, pilchards, salmon, cucumber, tomatoes, radishes, salad oil, vinegar, garlic, and mustard. I have also had to stop smoking, buying clothes, and going to the pictures

* * *

I support with enthusiasm the humanitarian suggestion to establish a regular column on diseases recently discovered not to exist. But a few questions come to mind How should priorities be assigned for the discovery that a well-known disease does not exist? The mere claim that one has never seen it should not suffice, but it is admittedly hard to *prove* that one hasn't seen it. Who discovered first, for instance, that the Frohlich syndrome does not exist? What kind of proof is acceptable for showing that a disease one has often read about *never* existed? How shall we deal with people who say "But I definitely remember a case I saw seventeen years ago "? Should young doctors be encouraged to discover diseases that do not exist? Can we encourage iconoclasm in an ancient and revered profession? Again, what shall we do about "diseases" that are common but confuse the doctor since they rarely make his patient ill, such as œsophageal hiatus hernia?

Meanwhile here are my suggestions for this week's list of diseases that should pass into history Bürger's disease, Van Neck's disease (ischiopubic osteochondritis), and calcaneal apophysitis in growing children with painful heels

* * *

The Island steamer was making its daily placid way from the mainland to the various island ports of call, and informal calls they were, and are, and (I hope) always will be

The group on the pier usually included the "post", the piermaster of course, often the police constable, and sometimes the nurse or doctor to collect polio vaccine. There is always the usual freight to be left—mails, bread from the city, newspapers, and miscellaneous household and farm goods of all kinds Some places have no pier—yet—and the ferryboat came out to meet us, rising and falling in the Atlantic swell when it left our side it was noticeably lower in the clear green water with its cargo of passengers, mailbags, and so on, and maybe a calf in a bag with its head showing I have seen a car too on the ferryboat and very cranky it looked.

At one of the smaller piers the duties of the piermaster, postman, brake-driver, rope-thrower, and handyman were combined in one person who was appropriately dressed in dungarees and wellingtons, a postman's jacket, and a taxi-driver's cap When we were ready to depart the Skipper leaned over the wing of the bridge and called down to him "Right, Dougie, let go" Down below on the pier, the foreshortened figure of the factotum—holding a struggling sheep between his legs—looked up and said plaintively "Ye're in an awful hurry the day, Hughie can ye no gie us a minute tae look round?" "You're just a damned nuisance Dougie," said the Skipper agreeably and began to fill his pipe while Dougie in rapid Gaelic exchanged news with the deckhands at the stern, and Her Majesty's mails waited till everyone had savoured the local gossip Then, and only then, did Dougie condescend to cast off

* * *

The first day's proceedings of the symposium were bearable because the organisers had thoughtfully arranged for a copy of *What's On In London* to be placed on each delegate's chair By the second morning, however, this literature had been enjoyed to the full and there was nothing for it but to listen to the communications or browse through the abstracts I felt obliged to sit through each session, if only to forestall the gibes of my adhesive colleague who delights in remarking on a late arrival or early exit. But on the last day, mercifully, the symposium split into double sessions, held in separate halls, and I was able to slip away unmolested to attend Dr Picasso's demonstration.

* * *

My peripatetic pardner had best get his facts strate afore he openz his noo Saloon. Wes Hardin was not at the O K. Corral, and Doc Holliday never dug no bullets out of him.

* * *

From a patient's card

Sept. 9—catheter in situ.
Sept. 10—catheter out of situ.

Rather like Mr Lumumba somehow, don't you think?

Letters to the Editor

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Dr Gordon (Sept 10) very reasonably expresses horror at the idea of feeding humans 1500 calories a day in the form of butter, and questions whether the animal experiments described by Dr Gresham and Dr Howard (Sept 3) warrant their implication that in man coronary thrombosis and coronary atherosclerosis are independent in their ætiology

I have recently completed an epidemiological investigation of coronary heart-disease in a population sample of over 220 men aged 65–85 years, and have come to the same conclusion as Dr Gresham and Dr Howard Very briefly my reason for this is that when these old men with symptomatic and electrocardiographic evidence of coronary heart-disease are compared with their coevals who do not have this complaint, they lack several of the characteristics which have been found [1–3] in younger men with coronary heart-disease They do not have higher serum-lipids, they do not smoke more cigarettes, nor have they expended less physical effort at work Recent research indicates that the most important factor in the pathogenesis of coronary heart-disease in young men is increased coagulability of the blood,[4] and that this is associated with a high serum-lipid level [5 6], high serum-lipids in turn occur in heavy cigarette smokers [7 8] but are reduced by physical exertion [9 10] Taken with epidemiological studies [11–14] this work suggests that most of the rise in mortality in coronary heart-disease is due to an increase in the incidence of acute coronary thrombosis, the often lethal condition of middle-aged men, but that coronary atherosclerosis without a major thrombus can cause chronic signs and symptoms later in life, that the former has been shown to be associated with disturbed lipid metabolism but the latter has not There is nothing new in this, nearly ten years ago Morris [11] theorised that a separate ætiology for coronary thrombosis and atheroma could be the only reasonable explanation for his finding that the amount of coronary atherosclerosis in the population has changed little over the past century, although mortality from coronary thrombosis has risen

It is impossible to express this argument logically yet succinctly (I hope a full report will be published early next year), but the important point is that laboratory investigation on the one hand and a field study on the other have led two independent groups of workers to the same conclusion for different—but I hope valid—reasons

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London, W C 1

ROY M ACHESON

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VIRAL ÆTIOLOGY OF MOUSE LEUKÆMIA

SIR,—I read with interest your recent survey [1] of vir tumours of mice [1] and I trust you will allow me to mal the following comments

In the initial experiments dealing with inoculation of filtrat prepared from leukæmic mouse tissues into newborn mice the C3H strain, it was observed in 1953 that some of t inoculated mice developed leukæmia, while others develop neoplasms of the parotid glands [2] It was relatively ea however, to separate that same year the respective causat agents by differential heating, ultracentrifugation, or use filters of different porosity, the leukæmic agent was larg heavier, and less resistant to heat than the parotid-tumo virus [2 3] Furthermore, it was later found that the parotid-tumo virus, but not the leukæmic agent, is resistant to ethyl ethe

The fact that the parotid-tumour virus is widely prevale in normal healthy mice was also established early in the studies [5] Many oncogenic viruses are carried by apparent healthy hosts, such viruses may remain latent through t lifespan of their carriers Some, however, become activat and cause neoplasms Such activation may occur spontaneousl or may be prompted by various factors, such as ionising radi tion, or certain carcinogenic chemicals A potentially leukæm genic virus is also widely prevalent in many normal mice Thu mice of the C3H or C57 Brown strains remain in most instance if undisturbed, free from spontaneous leukæmia Fractionate total-body X-irradiation will, however, induce leukæmia i some 50 to 60% of such mice From donors with radiation induced leukæmia the leukæmic virus could be recovered, an passed by inoculation to newborn mice, transmitting t disease [6]

Spontaneous activation of the leukæmic virus in mice occu now and then, and is particularly common in certain inbre strains of mice The parotid-tumour virus, on the other han remains as a rule latent when carried by naturally infected an undisturbed hosts Spontaneous development of parot tumours in mice is exceedingly rare Yet the development such tumours in natural carriers, such as non-inoculate C3H mice, could be prompted by treatment with cortisone or by total-body X-irradiation [8]

The recovery of infective and transmissible leukæmic viruse from natural mouse carriers is not always an easy matte Many such carriers, when used as donors, yield filtrates low infectivity, or no infectivity at all It was therefore considerable practical importance that a virus strain could b developed from spontaneous Ak leukæmia which now induce a practically 100% incidence of leukæmia following inoculatio into suckling mice of a susceptible strain such as C3H or C5 Brown/cd [9] Similar leukæmic mouse virus strains were als developed from transplantable mouse tumours [10 11]

I cannot agree with those [12] who question the viral natur of the leukæmia-inducing factor present in such filtrates Th leukæmogenic factor is a particle, which can be readily sedi mented in an ultracentrifuge [13] This particle is thermolabile and can be easily destroyed by heating to 56°C or even onl 50°C for 30 minutes [14] The particle is pathogenic, and induce a specific disease in susceptible hosts, its infectivity spectru is limited to certain species and even inbred lines of hosts Some of the leukæmic virus-strains recovered from, and carrie routinely in, mice can, however, also cross species barriers an cause lymphosarcomas following inoculation into newborn rats [15 16] After inoculation into susceptible hosts (i e., new-

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n or suckling mice of strains C3H or C57 Brown/cd) leukæmic virus strain developed in our laboratory [9] luces leukæmia in practically all injected hosts, it can then readily recovered from such hosts and passed indefinitely serial inoculations In normal C3H or C57 Brown/cd mice consistently induces lymphatic leukæmia If thymus is noved from inoculated hosts, the resulting leukæmia may pear later and be of the myelogenous form,[17] not previously served in mice of this strain Filtrates prepared, in turn, m donors with myelogenous leukæmia and inoculated into wborn C3H mice induced again the usual form of lymphatic kæmia [14]

The leukæmogenic factor present in such filtrates is a thermo-ile, self-reproducing, pathogenic agent, which can be n as a spherical particle less than 100 mμ in diameter in the ctron microscope,[18] and which, in all probability, belongs the broad group of oncogenic viruses

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LUDWIK GROSS

TUBERCULOSIS A SOCIAL STIGMA

SIR,—Mr Foster-Moore's letter (Sept 10) attracts my mpathy, as I had similar feelings (for similar reasons) any years ago

I can well remember, after a period of successful treatment, ling to secure an appointment because a medical officer on e staff I wished to join insisted (though he had never met e and sought no particulars) that he was not prepared to cept the risk of working with an " ex-T B " Fortunately, bsequent colleagues have been more enlightened, and I can sure your correspondent that the picture, now, is not as oomy as he paints it Though some prejudice certainly ists—and while patients who behave in the way he describes e with us some wariness is understandable—it is certainly ot generally true that ex-patients, if their disease is well ealed, " will never be able to obtain a position which involves medical check-up ", nor that " if a job is superannuated, ey have little chance of acceptance " As the medical officer f health responsible to my county authority for advising on cceptance or not of candidates for employment I can say that cal authorities in general (I cannot speak for all) are concerned only with two points (*a*) will the candidate be able to ive reasonably continuous service in the post for which he as applied ?, (*b*) is he likely to be a risk to those with whom e is to work ?

Naturally, one must apply stricter standards under (*b*) to urses, teachers, child workers, and so on, as is shown by the equirements of the Ministry of Education in respect of eachers, but to my personal knowledge there are now working n my county several teachers, nurses, child-care workers, and others who were accepted for service, under the superannuation scheme, after successful treatment for tuberculosis Incidentally, not one of these, past or present, has broken down in service since

An important point not mentioned by Mr Foster-Moore is life assurance Some companies refuse applications outright, others add a substantial loading to premiums, which becomes increasingly unreasonable as the years pass without any relapse One large company, however, who took me on many years ago, use the excellent method of a decreasing lien—i e, premiums are the same but the sum payable after death is substantially less than normal at first and gradually rises to the normal during a stated period For example, there may be a 20% lien running off in 20 years, after this period the full benefit is payable This method is specially suitable for those who have been tuberculous since it recognises the decreasing risk of relapse after the early years

One more point for your correspondent he should start with the firm intention that he will not attempt to hide, when making applications for posts, that he has had tuberculosis If his disease is well healed he will certainly be able to find an intelligent employer, and in any case it is not possible in practice to deceive many people

You will understand I do not wish to name my local authority, and I therefore ask permission to sign myself

C M O H

PARTIAL PARATHYROID INSUFFICIENCY

SIR,—In their interesting article of Sept 3, Dr Smith and his colleagues state that after thyroidectomy in which some of the parathyroids were removed there may exist a condition of latent partial parathyroid insufficiency, which could be made complete by calcium deprivation In my studies on the physiology of the parathyroids, from 1923,[1] in which the function of the parathyroids as regulator of the serum-calcium was established (and which seems to be forgotten by subsequent workers), partial parathyroidectomy in dogs (removal of 3 glands) produced a certain degree of partial insufficiency

The serum-calcium was lowered to a minimum of 7 1 mg per 100 ml without tetany, but was restored to normal in a few weeks on a diet which included half a litre of milk When the calcium-rich milk (0 6 g Ca) was removed from the diet, the serum-calcium fell in most instances, independent of whether the diet consisted of meat or bread, margarine, and fat, but not below the critical level producing tetany

It is interesting to compare this partial parathyroid insufficiency with the state of latent tetany produced by total parathyroidectomy in my dogs After a critical postoperative period with continuous calcium administration, the dogs passed into a state of latent tetany with adaptation to a low serum-calcium (about 6 mg) and behaved normally provided the diet contained half a litre of milk Whenever milk was removed from the diet, serious tetany ensued simultaneous with a further lowering of the serum-calcium Milk from which the calcium was removed had no protective effect When the calcium content of the milk was restored, tetany disappeared and the serum-calcium increased to the former (low) value

It was shown that life was possible without any parathyroids provided the diet contained a certain amount of calcium

Exactly the same observations were made in patients accidentally deprived of all (?) their parathyroids by parathyroidectomy [2] They adapted themselves to a low calcium level, and women even went through pregnancies and bore normal children when their serum-calcium was down to 6–7 mg But shortage of calcium in the diet always produced tetany

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BROILERS

SIR,—Your annotation of Aug 27 says that " [human] infections due to eating chicken meat seem almost unknown in Great Britain " An outbreak of salmonellosis due to food from a broiler shop has been investigated in this area and may be worth a brief description

On May 19 an elderly man with diarrhœa in an infectious-diseases hospital was found to be infected with *Salmonella thompson* This excited no comment because sporadic " thompsons " had been isolated fairly recently from two obviously unconnected persons But on May 21 a family of 4 persons and another 2 individuals were shown to be infected with *Salm thompson*, and on May 24 two families totalling 6 persons were all found to be similarly infected All had had foods from a certain broiler shop in the town where they all lived The manager of the shop and his assistant were examined and found to have *Salm thompson* in their fæces, and some cooked chicken sampled at the same time also yielded the organism, but other food from the shop—stuffing, roast pork, and shell egg—were all free The establishment, with the manager and assistant segregated, was closed.

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17 Gross, L *Proc Soc exp Biol*, *N Y* 1960, 103, 509
18 Bernhard, W, Gross, L *C R Acad Sci*, *Paris*, 1959, 248, 160

1 *Acta med scand* 1923, suppl vi
2. *ibid* 1930, 74, 13

In all, 35 persons were infected in this outbreak, the last case being found on June 6 7 persons had only a single positive swab, 25 persons averaged $3^1/_3$ weeks' infectivity, and 3 are still positive more than 3 months since original infection This outbreak was due to type 4, one of the two earlier sporadic thompsons had been type 10 *Salm thompson* is said to have been isolated from living broilers at a packing station that supplied this barbecue

The findings do suggest that in this affair the chickens rather than the manager were carrying the *Salm thompson* But how the organism escaped the consequences of cooking is a question Perhaps this infra-red cookery is less effective and penetrating than is claimed for it

Royal Infirmary,
Blackburn

M S SPINK

FAILURE OF CORTISONE TO CORRECT IMPAIRED WATER DIURESIS

SIR,—The letter from Dr Marks and Dr Hornabrook (Aug 27) on failure of cortisone to correct impaired water diuresis in patients with suprasellar tumours is interesting but might be even more so if further clinical and laboratory data were available

What was the clinical status of the patients, were tests of anterior pituitary function performed, and what were the plasma-cortisol levels? The fact that exogenous steroids failed to restore the diuretic response to normal suggests that adrenal cortical and anterior pituitary function were normal The authors conclude by suggesting " that in some cases of suprasellar tumour there is a failure to inhibit antidiuretic-hormone secretion in response to hæmodilution " Do they mean that the tumours have damaged osmoreceptors of the hypothalamicohypophyseal system (the presence of which was postulated by Verney [1]) but affected only the detection of hypo-osmolarity of the blood? The occurrence of such a condition would be at variance with the long-held view that injury to any part of the hypothalamicohypophyseal system results in diabetes insipidus [2] If the response to hyper-osmolarity of the blood is normal in their cases, then this would be the first clinical evidence to suggest that there are different osmoreceptors subserving the detection of hypo- and hyper-osmolarity

This is highly speculative but information from Dr Marks and Dr Hornabrook on the response of their patients to simple dehydration, to intravenous hypertonic saline or glucose, and to nicotine may throw further light on this problem

Their reference to H J Crow (footnote 2) should probably read "*Brit med J* 1955, ii, 401"

The New York Hospital,
New York 21, N Y

CRAIG D BURRELL

Bellevue Hospital,
New York 16, N Y

MARY E GRANGER

*** This letter has been shown to Dr Marks, whose reply follows —ED L

SIR,—I was interested to read the comments by Dr Burrell and Dr Granger on the observation that cortisone frequently fails to correct completely the impaired water diuresis in patients with suprasellar tumours which Dr Hornabrook and I described Although our findings are at variance with the long-held view that injury to any part of the hypothalamicohypophyseal system results in diabetes insipidus they are in agreement with the observations of others that impaired water diuresis may occur with suprasellar lesions with or without normal plasma-cortisol levels and urinary steroids [3] In a personal communication Dr D Marrack informs me that he has confirmed and extended our observations

The frequency of the abnormality described and the rarity of diabetes insipidus is demonstrated by the fact that u production was abnormally low after a 1500 ml water loa five of eight consecutive adult patients with craniopharyngio examined preoperatively Diuresis was normal in three one of these three there was evidence of secondary adre cortical hypofunction—mean resting urinary 17-hydro corticosteroid (17-O H C S) excretion was 3 mg per 24 ho with a normal rise after corticotrophin—and myxœdema to thyroid disease goitre with a normal thyroidal ^{131}I upt which was not increased by thyroid-stimulating hormo After replacement therapy with cortisone and triiodothyron there was a polyuria of 3–4 litres per 24 hours Mild to moder diabetes insipidus can be masked by coexisting adrenocorti hypofunction [4, 5] In these cases the water diuresis is norm despite clinical and chemical evidence of reduced glu corticoid secretion overt diabetes insipidus appearing wh cortisone therapy is instituted Despite the ability to produ a urine of specific gravity greater than 1 020 and a norm nicotine test, it is likely that in the case quoted above there w some impairment of antidiuretic-hormone (A D H) secretion als

WATER DIURESIS UNDER VARIOUS CONDITIONS IN A MAN OF 26 WITH A SUPRASELLAR TUMOUR (CRANIOPHARYNGIOMA) CONFI AT CRANIOTOMY

1500 ml water route of administration	Date	Therapy	Total 4 hr urine vol (ml)	% of dose	Commer
Oral	Dec 22, 1959	Nil	158	10 5 (75–120)	^{131}I uptake mal 17 K.S. 10 2 24 hr (8- 17-O.H C.S. mg /24 (6–21) Hb 13 3 g ml
Oral	Jan 15, 1960	Nil	90	6 0	
	Jan. 22	Cortisone 25 mg b d.			Course of X ray th begun
		„ „ „ „ „ „			Vision dete ating
	April 24	Cortisone 25 mg t.d s			
Oral	May 9	„ „	350	23	
1500 ml 5% dextrose intravenously in 65 min	*May 11*	„ „	*605*	*40*	*Moderate resis at 18*

Figures in parentheses are normal values for sex and age.

The nine patients already reported were investigated on th admission to hospital for the diagnosis and treatment of intr cranial disease In the main their general health was goo None had renal, hepatic, or cardiac disease Pituitary functi tests were carried out and included the measurement of urina neutral 17-ketosteroids (17-K S) and total 17-hydroxycortic steroids [6] and ^{131}I studies Plasma-cortisol levels were n measured

Pituitary function varied from moderate hypopituitarism three to complete absence of abnormality in two The fact th cortisone when given in doses not normally causing polyur but which are adequate for restoring water diuresis to normal hypopituitarism produced some, albeit incomplete, improv ment is further evidence that steroid deficiency was sometim a contributory factor

A man of 49 with moderate hypopituitarism caused by craniopharyngioma (17-K S 3 mg, 17-O H C S 3 5 mg, uptake 43%) excreted 17% of the water load before treatment A transient polyuria in which 2 litres of urine was excreted occurred within 12 hours of the first dose when steroid therap was instituted a few days later This was accompanied b a feeling of increased well-being The water-diuresis tes mained abnormal, however, when it was repeated while he is still on cortisone therapy and also after its replacement by ednisone

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[1] Verney, E B *Lancet*, 1946, ii, 739, 781, *Proc roy Soc* B 1947, 135, 25
[2] Fisher, D, Ingram, W R, Ranson, S W Diabetes Insipidus and Neurohormonal Control of Water Balance. Ann Arbor, Mich, 1938
[3] Hokfelt, B, Luft, R. *Acta endocr, Kbh* 1959, 32, 177
[4] Wise, B L. *J Neurosurg* 1956, 13, 107
[5] Unpublished observations
[6] Nabarro, J D N, Moxham, A., Walker, G *Brit med J* 1957, ii, 101

In another patient (cited by kind permission of Dr D arrack) with a craniopharyngioma there was a residual ability to respond to hæmodilution with a diuresis after onths of cortisone replacement therapy (see accompanying ble)

Generally in these patients fluid intake is voluntarily stricted and the urine is hypertonic The effect of deliberate id deprivation has not therefore been studied Nor has the fect of an intravenous hypertonic saline, or nicotine, fusion[7] [8] been studied regularly since brisk diuresis, upon e suppression of which the test depends, is seldom obtained Moderate diuresis often occurs during the night, some 2–18 hours after the ingestion of water For this reason we elieve that the hypothalamic secretion of A D H is still, to me extent, homœostatically controlled by the osmolarity f the blood

It is suggested that normally the neurosecretory cells in the ypothalamus elaborate and secrete A D H[9] and that they cease o do so when stimulated by impulses transmitted from the smoreceptors in response to hæmodilution (hyposmolarity) he similarity between this proposed system of A.D H regulation and the negative feed-back regulation of the pituitary rophins, whereby their production is suppressed by elevated lasma levels of the appropriate target-organ hormone, is pparent. Consequently it is unnecessary to postulate the eparate existence of osmoreceptors for the detection of hypersmolarity and hyposmolarity as suggested by Dr Burrell and r Granger

The osmoreceptors and the neurosecretory cells are believed o be anatomically distinct, the connection between them being ervous[10] Lesions of the hypothalamus which interrupt the eural pathways would thus cause a delayed, and impaired, uppression of A D H secretion in response to hæmodilution i.e., a release phenomenon) More extensive lesions, or small nes which damage the neurosecretory cells directly, cause iabetes insipidus Such lesions commonly occur after surgery, nd are commoner in children with craniopharyngiomas than n adults[5]

The results do not exclude the possibility of an irritative lesion causing hypersecretion of A D H by direct stimulation of the neurosecretory cells in the supraoptic and paraventricular nuclei[11]

Department of Chemical Pathology,
King's College Hospital,
London, S E.5

VINCENT MARKS

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—How discouraging to read Dr Cleobury's views (Aug 20) when he says that the open-door policy " has, in fact, been made possible only through the agency of modern physical methods of treatment " In fact open-door policies in mental hospitals antedate the modern physical methods of treatment by at least 60 years, as has already been pointed out in your columns[12]

The report of the Commissioners in Lunacy for Scotland for 1881 gives a very clear account of the successful institution of the open-door system[13] Adolf Meyer pointed out in 1894 that " Morningside in Scotland and other asylums show clearly that not a single door in any ward needs a lock " [14] The Peoria State Hospital in Illinois was completely open in 1906[15]

Of course opening doors by itself does not constitute treatment, it merely removes one of the irritating factors preventing recovery and provides a milieu in which a programme of rehabilitation and resocialisation can be effectively carried out

It has been repeatedly asked what caused the doors to be closed again I suggest that this was in part due to the very adoption by mental hospitals of the " time-honoured methods of clinical observation and study in conjunction with laboratory technique and research " so highly commended by Dr Cleobury, which tended to focus attention on the disease rather than on the patient, whose needs were apt to be forgotten

Leicester is only 40 miles from Nottingham Is there an iron curtain in between ?

Lincoln, Nebraska

FRANK WINSTON

ACQUISITION OF STAPHYLOCOCCI BY NEWBORNS

SIR,—The interesting article by Dr Wolinsky and others last week gives further point to my contention that nurses should wear gloves, of thin rubber and sterile, to overcome the ineffectiveness of ordinary hand-washing The authors do not state how to overcome this danger of spread " predominantly from the hands of the carrier to the infant " My letter[1] shows how to do it and why

Pathology Department,
St Margaret s Hospital,
Epping

FRANK MARSH

MORTALITY DUE TO BLOOD-TRANSFUSION

SIR,—I should like to compliment Mr Graham-Stewart on his interesting article of Aug 20, and to comment on his statistic regarding death-rates due to transfusions He stated " the mortality has been estimated as one to every 1000-3000 transfusions (Guynn and Reynolds 1958) This estimate was based on figures from leading (hospital) centres, and in hospitals as a whole the mortality may be higher " A review of the literature indicates that this figure is based on studies dating from 1917 to 1941, as the following synopsis will show

This particular statistic of one death from every 1000 to 3000 transfusions has been frequently quoted Checking article references, I found that in the February, 1958, issue of *Surgical Clinics of North America*, Guynn and Reynolds (p 19) and Gibbel (p 45) both used this figure Their reference was an article by C V Moore.[2] Moore's figures are based on statistics compiled by A S Wiener (*Blood Groups and Transfusions*, 1943) and Kilduff and De Bakey (*Blood Bank and the Technique and Therapeutics of Transfusions*, 1942) They based their mortality-rates of 1 death in every 1000–3000 transfusions on studies dating back to 1917

I have therefore attempted to determine a current valid statistic regarding death-rates from blood-transfusions Information from the Ministry of Health and Blood Transfusion Centres reveal that over 3,500,000 units of blood were issued to the various hospitals in England and Wales for the five years 1954–58 According to statistics in the Registrar General's *Statistical Review of England and Wales*, there were only 8 deaths due to blood-transfusions reported during this period. If we assume that as much as 20% of the blood issued was not used, there were 8 deaths in 2,800,000 transfusions—1 death in every 350,000 transfusions

In my own country, the United States, the Bureau of Vital Statistics recorded 234 deaths due to blood-transfusions in 1957 and 1958 During these two years, approximately 6,000,000 transfusions were given Therefore, there was 1 death in every 256,000 transfusions

It is encouraging to note that deaths from blood-transfusions are relatively rare today From the above data, it can be estimated that there is 1 death in every 250,000 to 350,000 transfusions It is not my meaning, however, to infer that I condone the indiscriminate use of blood-transfusions These comments are offered as a clarification of the current mortality-rate from blood-transfusions and to erase the use of statistics which date from 1917

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[7] Cates, J E., Garrod, O *Clin Sci.* 1951, 10, 145
[8] Lewis, A. A. G , Chalmers, T M *ibid* p 137
[9] Bargmann, W *Endeavour*, 1960, 19, 125
[10] Landgrebe, F W , Ketterer, B , Waring, H *in* The Hormones (edited by G Pincus and K V Thimann), vol III, p 395 New York, 1955
[11] Andersson, B , McCann S M *J Physio* 1955, 129, 44P
[12] Gibson J *Lancet*, 1954, ii 1017
[13] Tuke D H. *in* The History of the Insane in the British Isles, pp 376–378 London, 1882.
[14] Report to the Governor of Illinois Springfield, Aug 2, 1894
[15] Pollak, M , Baer, W H *J Hist med* 1953, 8, 56

[1] *Lancet*, 1958, ii, 588
[2] *J Amer med Ass* 1952, 149, 1613

London, S W 5 J HARRIS JOSEPH

DISPOSABLE UNDERPADS FOR INCONTINENT PATIENTS NURSED AT HOME

SIR,—The letter of July 23 by Dr Roberts and Miss Mann interested us not merely because we too manufacture disposable incontinence pads, but also because it is possible to use them with greater saving in cost than your correspondents indicated

The size of the pads mentioned, 30 × 23 in, is larger than may always be necessary, and for this reason we make pads of 24 × 16$^1/_2$ in Purchased in bulk, they cost approximately 4½*d* each. From this it will be evident that, in a great many cases, it is far more economical to use such pads than to launder soiled linen Where larger pads are required, there is perhaps little actual saving in money but a considerable reduction in labour With smaller pads, there is economy in both ways

Wheat Bridge Mills,
Chesterfield

N P MANN
Development Manager, Robinson & Sons, Ltd

SIR,—Incontinence pads have been used in the geriatric unit at Stobhill General Hospital since 1955 I understand that since 1957 they have been available in Scotland to general practitioners on prescription form E C 10

The pads are available in two sizes—12 × 16 in and 16 × 18 in—and are made of cotton-wool, cellulose, and non-absorbent grey wool The pad is covered in gauze in order to prevent it adhering to the patient's skin The cost to the hospital is approximately 6*d* for the smaller size and 8*d* for the larger size I have been very satisfied with the type used.

The makers are Smith & Nephew—Southalls Ltd, 5, Singer Street, London, E C 2

Geriatric Unit,
Stobhill General Hospital,
Glasgow, N 1

W FERGUSON ANDERSON
Regional Adviser in Diseases of Old Age,
Western Regional Hospital Board (Scotland)

PERITONEAL SPLASH A PHYSICAL SIGN

SIR,—It is sometimes difficult to differentiate between perforated peptic ulcer and perforated appendicitis Examination by radiography before operation is invaluable, but in certain circumstances may impose delay, and even expense, on a patient in pain The differentiation is important, because the correct placing of the incision makes surgical treatment of either condition easy

To be able to demonstrate diminished liver dullness is useful, but there is a wide variation of the normal area of liver dullness There is, however, an additional physical sign which can demonstrate the presence of air in the peritoneal cavity The rigid abdomen of the patient relaxes under a general anæsthetic, and allows the contained free air and fluid to give forth a splash, if vibrated The splash is not so localised as that of an intragastric succussion splash, and has a note more highly pitched, and more superficial

As an example of the value of this physical sign, I would cite a recent case treated for Dr J A Smart in the Victoria Hospital at Lewes, a general-practitioner hospital with good radiological facilities, but without resident staff A young man was admitted suffering from severe abdominal pain, which had settled in the right lower abdomen The history and physical signs were equivocal, but it was clear that operation was indicated Anæsthesia was induced by Dr H Rice, and the abdomen was exposed on the operating-table The sponge-holding forceps with the swab soaked in antiseptic was agitated gently but rapidly on the skin of the relaxed abdomen, a splash was elicited, and all doubts were solved. A perfor duodenal ulcer was patched through an upper midline inci and the patient recovered quickly

I have read no description of this sign, which hel in the management of this and other patients, therefore ask you to publish this letter

Hove P A LANE ROBERT

HYDROCORTISONE INHALATION IN ASTHM

SIR,—Dr Langlands and Dr McNeill (Aug 20) re that hydrocortisone by inhalation did not improve lung function in their 10 asthmatic patients They 15 mg per day by 'Medihaler', and they were awa although this is not mentioned in their paper—" tha to 50% of this amount may have been wasted " (pers communication) In my opinion, the medihaler techn may cause even greater wastage Attention sh therefore be drawn to the possibility that their nega result, which is in contrast to that of other author may be due to insufficient dosage

London, N.3 H HERXHEIME

SMOKING BY ADOLESCENTS

SIR,—Most doctors who have looked at the evid must be convinced that children who start smoking exposing themselves to a serious risk of lung cance later life If they live in an industrial area in Engl they also risk developing chronic bronchitis

In our society we often prevent people from do things they want to do, if it is agreed that the propo action would be harmful to the doer, for example, we to prevent people from committing suicide, becom morphine addicts, or marrying under the age of Nevertheless very few doctors have suggested that should prevent adolescents from smoking if they want and most people will approve, freedom should not lig be curtailed

However, I for one find it difficult to understand w we allow freedom to the tobacco manufacturers to sp very large sums of money on advertising which is dire opposed to the truth as we know it Much of t advertising is, moreover, directed by subtle psycholog means to appeal to the fears and hopes of adolesce As I see it, this kind of advertising is a systema attempt to mislead the young for personal gain It really very difficult to know how to answer a fifteen-ye old boy who asks " If smoking is as bad as you say, w don't the doctors tell the Government to stop cigar advertising ? "

Halstead, Essex. R E W FISHER.

Medicine and the Law

Death after Wasp Sting

AT an inquest at Woodbridge, Suffolk, on a 68-year- woman who died shortly after being stung by a wasp, it w stated that she had also been stung about a month earlier, wh the only ill effect was swelling of a finger[4] After receiving t sting which led to her death the woman complained of feel faint and she started to tremble A doctor was called, a within minutes adrenaline was administered, but the pati nevertheless died. A pathologist testified that the cause death was anaphylactic shock, the patient having been sensiti by the earlier sting A verdict of death by misadventure w recorded

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1 Brockbank, W, Pengelly, C D R *Lancet*, 1958, i, 187

2 Helm, W H., Heyworth, F *Brit med J* 1958, ii, 768

3 Herxheimer, H., McAllen, M. K., Williams, D A *ibid* p. 762

4 *East Anglian Daily Times*, Sept. 15, 1960

Obituary

JOHN FOSTER GASKELL

M.A., M.D. Cantab., F.R.C.P., D.P.H.

Dr John Gaskell, who died on Sept. 11 at Cambridge at the age of 82, had never engaged in private practice, but had chosen to remain for over twenty-five years an honorary physician and pathologist to Addenbrooke's Hospital.

The son of a distinguished Cambridge physiologist, W. H. Gaskell, F.R.S., he was educated at Marlborough, Caius College, Cambridge, and St. Bartholomew's Hospital. After qualifying in 1907 he held a house-appointment at Barts, and in 1911 he was awarded a Beit fellowship. For a time it seemed that he might follow his father in physiological research, for in 1913 and 1919 he published important papers on the suprarenals and on the sympathetic nervous system. But his acceptance of a demonstratorship in pathology at Leeds University gave a hint of what was to follow, and the rest of his publications were on pathology and experimental pathology.

In the 1914–18 war he built up in Salonika a much-needed bacteriological service, and his book, written jointly in 1916 with Michael Foster, the younger, on cerebrospinal fever is probably the best known and the most outstanding of his works. Cambridge contemporaries will also recall how, during a comparatively quiet spell in the war, he turned his R.A.M.C. unit into an amateur operatic company, and with the help of his brother officers, Dr. Ffrangcon Roberts, Dr. Charles Budd, and other Cambridge doctors, he staged a full-scale production of *The Mikado* which was so successful that it went on tour.

On his return to Cambridge in 1920 Gaskell was elected assistant physician and pathologist to Addenbrooke's Hospital. He was largely responsible for the early development of the pathological services there, taking an active part in the routine work, especially morbid anatomy and histology, until he retired in 1946. He published a series of papers on lobar pneumonia in which he carried the American work on experimental pneumonia a stage further by showing that it was the virulence of the pneumococci—which he could vary at will by mouse-passage—rather than the size of the infecting dose reaching the lung that decided the type of lesion produced. This work, which was the subject of his Bradshaw lecture to the Royal College of Physicians in 1927, threw much light, not only on the pathology of lobar pneumonia, but also on the localisation of the lesions in bronchopneumonia and terminal pneumonia.

C. H. W. writes:

"The double post of physician and pathologist, which was still practicable in those days, gave Gaskell insight into, and a wide knowledge of, the problems of disease—qualities which were invaluable to all those who worked with him or were taught by him. He was a physician of the old school who insisted on the importance of careful history-taking and thorough clinical examination. He had a dry humour and was curiously detached from the hurly-burly of modern life. He disliked innovations, and, being unmechanical, he endured rather than enjoyed the austere rides on his motor-cycle to and from work. He continued to live, so far as he was permitted, in the tranquil atmosphere of the Edwardian era. It suited his temperament, but no doubt it was partly the result of his inheriting the home of his childhood, a fine estate with beautiful terraced gardens on the chalk hills near Cambridge. This was the centre of his life and its purpose was to provide a home for his daughter and his three grandchildren on their frequent visits from abroad. He found fulfilment in his work on the soil until his strength failed only a few months before his death. We who are left feel that his passing marks the end of an epoch, characterised by weekends spent in cutting trees or playing tennis, in an atmosphere of serenity and spacious beauty.

"The sudden death in early childhood of his only son, and two years later of his wife, left a permanent mark, detectable perhaps in his somewhat reserved manner. But behind this lay a sensitive nature and a warm heart, and all who met him knew instinctively that this was a man of integrity and a trusty friend."

ERNEST KENNETH MACDONALD

O.B.E., M.D. Lond., D.P.H.

Dr. E. K. Macdonald died on Sept. 13 in Leicester, where he was medical officer of health till his retirement earlier this year.

During the 1914–18 war he served as a surgeon sub-lieutenant and qualified from St. Bartholomew's Hospital in 1919. After a period in general practice he became an assistant medical officer of health in the public-health department of the London County Council, and in 1926 deputy M.O.H. for Barnsley. He was in turn M.O.H. for Keighley, Barnsley, and Stockport before he was appointed to Leicester in 1935.

Dr. Macdonald regarded the National Health Service Act as a challenge which offered chances of fruitful work to the public-health service. He particularly welcomed the opportunities it offered for health education, and a health education officer was early appointed in Leicester, and a continuous programme of health education developed. Dr. Macdonald produced an excellent colour film on the health services of the city. Most of the film he shot himself, and he spoke the commentary. Another useful method of disseminating information was the cartoon figure of "Dr. Fosse" (Leicester is on the Fosse Way), who was used to give advice on health subjects. Dr. Macdonald also recognised the possibilities of a good home help service. In Leicester all home helps were given a fortnight's training and good indoor and outdoor uniforms, and the social value of their work was stressed. Home helps were provided without charge for certain problem families.

Dr. Macdonald was for many years interested in deafness, and he invited the Ewings of Manchester to Leicester to see what might be done there to ascertain deafness early in young children. Sir Alexander and Lady Ewing were quickly convinced of the value of health visitors in this work, and a pioneer clinic for the ascertainment of young deaf children and their training was established in the city.

Dr. Macdonald's work in Leicester soon won him a reputation outside the city and he was asked to sit on many national committees. He had been, for example, a member of the Radium Commission, of the Ministry of Health Prevention of Blindness Committee, of the Ministry of Works Advisory Council on Building Research and Development, and of the committee controlling the Public Health Laboratory Service. His chairmanship of the Central Council for Health Education from 1948 to 1951 included the difficult transitional time when its finances were reorganised and local authorities came to play a larger part in its running.

A. I. R. writes:

"Dr. Macdonald had more than his share of bad health, but nothing daunted his spirit or affected his elan. A dynamic personality and leader, he was always full of energy, applying his very quick brain to problems which were brought before him, quickly familiarising himself with what might be new and finding a solution. He was a most cheering person to work with. A first-class administrator, he always seemed to be a step ahead of most people in his ideas and means of putting them into practice. Until illness restricted his activities he had led a most active life—surf-riding, sailing, playing badminton, caravanning He was also a competent photographer and a keen gardener "

Dr Macdonald leaves a widow and three daughters, two of whom are doctors

ALBERT VICTOR JOHN RICHARDSON

K B E , C B , B A , M B Dubl , D P H

Air Marshal Sir Victor Richardson, who was director-general of the Royal Air Force Medical Services from 1938 to 1941, died on Sept 16 at the age of 76

He was the son of Lieut -Colonel T F Richardson of the 5th Royal Irish Fusiliers, and he was educated at Trinity College, Dublin After graduating M B in 1908 he entered the Royal Navy During the 1914–18 war he served with the R N Air Service and ultimately transferred to the Royal Air Force when it was formed In 1919 he was already a wing-commander, and in the same year he was appointed O B E After successive promotions he had reached the rank of air vice-marshal when he was appointed director-general of the R A F Medical Services in 1938 He held this appointment in difficult years of expansion and anxiety, but under his guidance the service effectively coped with heavy responsibilities He was promoted K B E in 1939 After he retired he became chief casualty services officer at the headquarters of the London Civil Defence region, and he held this post till the end of the war

Sir Victor Richardson was twice married His first wife, by whom he had two daughters, died in 1929 His second wife, formerly Miss Eileen Hornibrook, survives him with a daughter

Sir GORDON GORDON-TAYLOR

F G B writes from New Zealand

" I first met Gordon-Taylor in 1916 during the Battle of the Somme, and thereafter till the end of the war our paths often crossed in the clearing-station zone and my regard and affection for him steadily grew During the Passchendaele fighting of 1917 I was attached to a forward group of clearing stations at Brandhoek near Vlamertinghe and visiting surgical teams included Ernest Miles, C H Fagge, Rock Carling, and Gordon-Taylor To live and work with older men of such high quality was a privilege and an education to juniors like myself, *and of them all Gordon-Taylor stood pre-eminent,* partly because of his surgical distinction and partly because of his innate kindliness, sympathetic understanding, and appreciative attitude towards the younger men in short, he was like a respected and much admired elder brother, someone to emulate

" Later on he came to New Zealand and Australia as anatomist to several visiting teams of examiners for the primary fellowship Then in 1945 he visited us on a good will tour, which was more in the nature of a royal progress I am sure the warmth of his welcome must have afforded an intense gratification to his modest and responsive heart No British surgeon was better known to us and none could have provided a happier link between the old and the new The key to his supremacy lay, as it did in those far distant war days, in his obviously genuine sympathy and understanding of the problems of younger men, and no one was quicker to give praise when due His friendships ranged from contemporaries down the scale to examination candidates who became his friends overnight and sought his advice in their careers I write this as a personal tribute to a dear and ever kind friend and I know that it expresses the feelings, in some part at least, of many others If fate denied him the Woolsack, as he termed it, he had a more solid satisfaction in the affectionate regard of countless friends and admirers "

Dr MARJORY WARREN

M L I writes

" The news of Dr Warren's death has come as a profound shock to all who are connected with geriatrics Besides those who actually worked with her, many, like myself, who were trying to develop medical services for the aged, knew that we could always go to her with our problems and be sure of sympathetic and helpful advice, given freely with all the authority of her long experience We came away encouraged by her support to return again when faced by another set of difficulties, certain to benefit once more from her warm interest and unbiased approach "

J S, one of her colleagues at the West Middlesex Hospital, writes

" Dr Warren had spent virtually the whole of her professional career in the hospital service When she came to the West Middlesex in 1926 her duties at first covered the whole of medical practice and it is believed that her inclination was then towards a surgical career It soon became apparent to her that, though the elderly and chronic in her charge were well cared for and well nursed, much more could be done to help them to return to an active and useful life Her interest in geriatrics was thus born at an early age, and she began to give more and more of her time to this pioneer work and made a number of valuable contributions to its literature

" The war gave an impetus to this work, and, when peace came, as the specialty of geriatrics came increasingly to the front, she played an increasingly active part both in this country and abroad But it was to her own hospital that her life's work and affection were chiefly given. To her department came visitors from all over the world and she trained a large number of doctors in her methods Possessed of an attractive manner and strong personality, she was quite fearless in putting forward views which she considered right and did not hesitate to take a lead in righting wrongs however unpleasant the task might be She seemed so full of life and energy and was quite tireless Her death has been a heavy blow not only to her colleagues but to countless patients who have lost a devoted friend as well as a beloved doctor "

Appointments

Anderson, A M., M B Edin , D P H M O , headquarters staff, South Eastern Regional Hospital Board, Scotland
Gillie, Anne K , M B Glasg , D P M assistant psychiatrist (S.H.M.O), *Clifton Hospital, York*
Juel-Jensen, B E , B M Oxon., Cand med Copenhagen M.O , United Oxford Hospitals
Lubin, M M , M B Lond senior casualty officer, County Hospital, Lincoln.
Mellor, M R , M B Birm assistant M O H and school M O , Newcastle upon Tyne
Robertson, J D , M D Edin , F R C P E , F F A R C S , D A consultant, department of anæsthetics, Royal Infirmary, Edinburgh
Spaul, G F , M B Lond , D P M senior assistant psychiatrist, Coppice Hospital, Nottingham

East Anglian Regional Hospital Board

Chaudhary, G A , M B Punjab registrar in geriatrics, West Suffolk Hospital group
Huntsman, R. G , M B Cantab , M R C P consultant pathologist, Peterborough, Wisbech, and King s Lynn hospital areas
Kapur, S K , M B Nagpur, D T M & H medical registrar, Papworth Hospital
Raverty, S J , L R C P I registrar in psychiatry, Suffolk mental hospitals.
Turner, R. G , M B Glasg registrar in plastic surgery, regional burns and plastic surgery unit, West Norwich Hospital.

Manchester Regional Hospital Board

Davidson, I W , M B St And , F F A R C S , D A. consultant anæsthetist, North Manchester, Booth Hall, and Monsall groups of hospitals.
Dowie, Robert, M B Edin., M.R.C.O G consultant obstetrician and gynæcologist, Barrow and Furness group of hospitals
Hallack, I M , M B Cape Town, F F.A. R.C.S , D.A. consultant anæsthetist, Salford group of hospitals
Peck, R M , L.A H Dubl senior casualty officer, Royal Albert Edward Infirmary, Wigan
Ross, W J , L.R.C.P E senior casualty officer, Victoria Hospital, Blackpool
Swithinbank A. H , M.B Lpool, F R C S , D A. consultant general surgeon, Wigan and Leigh group of hospitals

Notes and News

CHILDBIRTH HERE AND IN U.S.A.

"EXPLORING each other's point of view" may be described as the aim of the newly founded Anglo-American Society, whose first meeting took place in Cambridge on Sept. 7. The officers took care to explain that it was founded "not to duplicate existing societies, not for British doctors to invite American friends, but as a common enterprise by both, to promote social and professional liaison, and to examine attitudes, values and customs as they apply to medicine in both countries."

The aim was admirably met in the controversial subject, the Normal Pregnancy on Both Sides of the Atlantic, discussed under the chairmanship of Major JOHN HOLBROOK (Lakenheath).

Two main speakers presented the obstetric picture for Britain. Dr C. R. F. MALLET (Ipswich) described the pre-eminent role of the G.P.-midwife liaison. "The midwives," he said, "are the backbone of obstetrics. Their skill and competence is very, very good, we rely on them throughout." But he said that "a cardinal point to bear in mind is that consultant advice is readily available at all times in the home or in the hospital, and that in emergencies there is always a bed in hospital." Dr Mallet's summary covered all the features familiar to his British colleagues (though murmurs showed that not all of them agreed with his dismissal of routine weighing as of little value). In particular he made it clear that most doctors gave considerably more detailed supervision than is paid for by the National Health Service obstetric service rules. The role of the general-practitioner obstetric unit and especially of domiciliary delivery were of special interest to the Americans in the audience, as was the work of the flying-squad. They noted also the allowance to the mother of £17 10*s.* or £12 10*s.*, for *domiciliary or hospital deliveries* respectively, and the current N.H.S. fee of £7 7*s.* to the doctor for his obstetric services.

Mrs S. MEE, Cambridgeshire's county nursing officer, described the training and work of midwives. She pointed out that, on top of the full nursing training, these women had six months' specialised hospital and then six months' domiciliary work. "It is no part of their training to attend to abnormal midwifery, but they do see these abnormal cases and they learn to recognise them if they arise." As soon as an abnormality was found the doctor was notified. Mrs Mee explained the close cooperation with the doctor, the restricted range of drugs that midwives could use personally, and the safeguarding machines which controlled the strength of nitrous oxide or trichlorethylene given. The work, she said, was very personal, covering antenatal and puerperal attentions as well as the delivery. Each midwife was deemed capable of coping with sixty mothers a year, and this figure was more or less maintained. England and Wales had some 16,500 midwives in actual practice, and great attempts were being made to increase this number.

Dr DAVID PETERSEN (Lakenheath) gave the transatlantic view with verve and friendliness. Perhaps what most surprised his British colleagues was his statement that the United States had but five hundred midwives, and five schools for them. This small band were either training as supervisors or instructors or destined for work in mission fields or very remote areas.

On domiciliary delivery Dr Petersen was polite but adamant. He deplored it. He taught the belief that if the obstetric emergency needed a hospital bed, then the patient should already have been in that bed. A number of emergencies always would occur in the twinkling of an eye. To sort out in advance those women needing hospital and those fit for home deliveries was not enough. Many a consultant might make an error in such evaluation, and all the more easily could the less specialised doctor.

American babies, then, were hospital-born, and this could happen in one of three ways. If the mother was indigent she could be treated as a charity case, through hospital clinics and wards. If she could pay she was looked after by family doctor in a hospital which allowed him this privilege. Or she could choose to be dealt with by the specialist obstetrician and so get not only his expert attention, but perhaps also a little status symbolism. Delivery by specialists was becoming more common, with patients less and less ready to accept the family doctor. "The kindly old doctor is passing from the scene just like the buffalo and the Indian."

When the patient was admitted in labour the nurse mainly checked the details of admission, and the patient was the doctor's. Episiotomies and low forceps were common. Once the baby had been born, and after twelve hours of rest, the new mother was extracted from her bed and considered to be fully ambulant. She remained three to five days only in hospital.

Dr Petersen answered some pointed questions. He conceded and regretted that after she left hospital the mother had little close medical or nursing supervision. As to whether the patient's income affected the length of stay in hospital or the treatment given, he said: "We try not to let the financial influence our good judgment," but put a hesitant stress on the word "try." He was lukewarm on relaxation in labour, but "prepared to go along with such a plan if the patient was in quest of such discomfort." On the other hand, obstetric analgesia was very highly developed, with, he thought, far greater variation than in Britain since all obstetrics had hospital facilities.

Finally, he remained unconvinced about the role of the midwife. "I do not believe," he said quizzically, "that the best obstetrics can be practised with the doctor at home in bed." Yet in spite of the contrasting methods on each side of the Atlantic the figures for maternal and fœtal mortality and morbidity showed no significant differences.

In the discussion that followed, Captain MARTIN ROSNER showed himself moved by the British maternity allowances and also by the N.H.S. obstetric fees. "I find it rather paradoxical," he said in mock bewilderment, "that the patient gets paid more than the doctor does."

CHARTERED SOCIETY OF PHYSIOTHERAPY

DURING the annual congress of this society, opened in London on Sept. 15 by Sir Robert Platt, P.R.C.P., a dinner was held on Sept. 16.

Dr T. F. Fox, proposing the Society and its Founders, said that the latter would be happy to see how large the society is, to attend the congress illustrating the remarkable scope of its work, and to know that the professional status physiotherapists have long enjoyed is now to have statutory recognition. Miss Sybil Evans, responding as vice-chairman of council, pointed out that people with severe handicaps are no longer confined to bed or a cripple's chair, and physiotherapists were continuing their study of the part physiotherapy can play in preventive medicine, especially in the study of posture and lifting. State registration had been their object for forty years, but the profession had insisted on its right to self-government, with a majority of physiotherapists on the registration board. Though "the medical profession as a whole has not seen eye to eye with us here", physiotherapists were grateful for the continuing practical interest of doctors not only in the counsels of the society but in physiotherapy departments and schools.

Sir Cecil Wakeley, the president, welcomed The Guests, and Sir Arthur Porritt, P.R.C.S., replied. Pleading for more attention to the medicine of sport, he gave some account of the medical side of the recent Olympic Games, and spoke warmly of the determination of physiotherapists to work as members of the medical team.

Miss Evans paid a special tribute to the work of Sir Harold Boldero as chairman of council during six difficult years. The society was indebted to him for the great patience with which he had presided over a body of individualists, and for the help he had so willingly given wherever it was needed. "We have a great affection for you, and I can say that now."

The Founders' lecture was given on Saturday by Lord Taylor, F.R.C.P., who spoke on the Future of Physiotherapy. Other lecturers included Dr Victor Dubowitz, Dr Helen Dimsdale, Mr Walpole Lewin, Mr A. J. Evans, and Dr J. Delargy.

UNSUITABLE FOR SCHOOL

The procedure under the Education Act, 1944, for the care and training of mentally handicapped children will be modified by some sections of the new Mental Health Act which come into force on Nov 1 In a circular to education authorities Sir David Eccles, the Minister of Education, says that they will extend the rights of parents, who will in future be able to require local education authorities to review, after a year, a decision that a child is unsuitable for education at school, and to appeal to the Minister on the result of the review The procedure for arranging the medical examination of these children is simplified New provisions are made to ensure consultation between education and health services, and the education authority, when they formally notify the parents that the child is unsuitable for an ordinary school, must now explain what the local health authority can do for his treatment, care, or training Much of the success of the new arrangements will depend on cooperation between the health and education services, and the Minister considers that it would be helpful if the doctor who examines the child were acting for both authorities

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University of London

Dr R J Goldacre has been appointed to a readership in cell physiology tenable at the Institute of Cancer Research Royal Cancer Hospital

University of Leeds

A series of lectures for registrars and senior house-officers will be held at the General Infirmary at Leeds at 5 P M and 6 P M on Wednesdays starting on Oct 5 The speakers will include Miss U M Lister, Sir Andrew Claye, Mr J B Farquhar, Mr T F Redman, Mr Herbert Agar, Mr G W Theobald, Dr R R Macdonald, and Mr D W Currie The fee for the series will be £3, and further information may be had from the sub-dean, School of Medicine, Thoresby Place, Leeds, 2

University of Glasgow

Dr John Milne has been appointed McCall Anderson lecturer in dermatology He will be in charge of the dermatological department at the Western Infirmary

World Health Organisation

Dr Louis Verhoestraete has taken up his appointment as director of the division of health protection and promotion at W H O headquarters in Geneva This division, which was created recently in a reorganisation of the headquarters services, covers cancer, cardiovascular diseases, dental health, mental health, nutrition, and social and occupational health

Dr Verhoestraete has been chief of the health promotion branch of the Pan-American Sanitary Bureau in Washington, which is also a W H O regional office, since 1954 He was born in 1912 in Belgium, and took his medical degree at the University of Louvain From 1942 to 1947 he was a provincial adviser for the Œuvre Nationale de l'Enfance of Belgium In 1947 he made a study tour in the United States, and the same year he joined W H O 's staff as a consultant in pædiatrics with the United Nations Children's Fund in Paris In 1950 he became chief of maternal and child health at W H O 's Geneva headquarters He received the degree of master of public health from Harvard University in 1954

Hospital Appointments in France

The Collège de Médecine des Hôpitaux de Paris has made arrangements for young doctors from other countries to hold junior hospital appointments in Paris

The posts can be held for 1–3 years The salaries and allowances paid are those of French *internes* Candidates must have passed their qualifying examination in medicine and had 2 or 3 years' experience They must also have a good knowledge of French Applications are now invited for appointments for the year beginning Oct 1, 1961 Further details can be had from the scientific office of the French Embassy, 22, Wilton Crescent, London, S W 1

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty on Sept 5, the following were admitted to the fellowship

Nalkunda Kyathappanavara Channappa, Gulamabbas Juma Ebrahim, Abraham Galea, A J Graham, J A Hynes, A H Laing, W M McCrae, Keshab Chandra Mallick, Tahir Abdel Mahmoud Rahman, *qua* physician, Abdul Khaliq, Badr Ul Islam Pirzada, W H Reid, *qua* surgeon.

A conference on accident surgery is to be held from Nov 30 to Dec 2 at the faculty, 242, St Vincent Street, Glasgow, C.2 Particulars will be found in our advertisement columns

Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arranged by Dr Joseph Smart on Fridays from Sept 30 to Dec 16 Open lectures will be given on Wednesdays from Oct 5 to Dec 14 by Dr J R Bignall, Dr R W Riddell, Dr V Springett, Mr O S Tubbs, Dr W D W Brooks, Dr Paul Wood, Dr J N Pattinson, Mr T Holmes Sellors, Dr H Nicholson, Mr M Paneth, and Dr J R May All the lectures will be held at 5 P M at the institute, Brompton Hospital, Fulham Road, S W 3

British Postgraduate Medical Federation

The inaugural lecture of the 1960–61 series on the scientific basis of medicine will be given by Prof C H Waddington at 5 30 P M on Thursday, Oct 20, at the Senate House, University of London, Malet Street, W C 1 His subject will be the significance of developmental biology

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A service for doctors is to be held in All Souls Church, Langham Place, London, W 1, on Sunday, Oct 16, at 11 A M Sir Arthur Porritt and Sir James Paterson Ross will read the lessons Doctors who wish to reserve seats for the service should write to the church secretary, who will also issue tickets (*7s 6d*) for a buffet lunch which is to be held after the service at the Royal Society of Medicine

Mr Leslie Farrer-Brown will give the inaugural address at the medical school, University of Birmingham, on Monday, Oct. 3, at 3 P.M

The Chest and Heart Association is to hold a symposium on asthma on Wednesday, Nov 2, at 4 30 P M , in Edinburgh Tickets (21*s* each) may be had from the Association, 65, Castle Street, Edinburgh, 2

A symposium on hæmatology for general practitioners is to be held at Addenbrooke's Hospital, Cambridge, on Saturday, Oct 1 Further particulars may be had from the secretary of the Medical School, Tennis Court Road, Cambridge

The Association of Clinical Biochemists and the Association of Clinical Pathologists will hold a scientific meeting on Saturday, Oct 1, at 9 30 A M , at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W C 2 The meeting will include a symposium on malabsorption

The next meeting of the Osler Club of London will take place on Tuesday, Oct 11, at 8 15 P M , at the British Museum, when Sir Frank Francis, Dr W S C Copeman, and Mr W T Stearn will speak on Sir Hans Sloane

The annual meeting of the North of England Otolaryngological Society will be held in Bolton on Saturday, Oct 1, at 2 P M.

Dr G R Sharp has been appointed to an Imperial Chemical Industries fellowship to do research under Prof C F W Illingworth, Prof R C Garry, and Dr H H Pinkerton, on respiratory physiology and anæsthesia in the department of surgery at the Western Infirmary, Glasgow, where an oxygen pressure chamber has recently been installed

The annual dinner for past and present students of the Middlesex Hospital Medical School will be held at the Savoy Hotel, London, W C 2, on Friday, Sept 30, at 7 30 P M A refresher course will be held on Friday and Saturday, Sept 30 and Oct 1, at the hospital Further particulars may be had from the medical school secretary

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CORRIGENDUM *Too Few Doctors* —Our annotation of Sept 3 said " The Willink Committee suggested that the maximum list should be reduced without undue delay to 2500 in non-rural areas and to 2000 in rural areas " This was an incorrect reading of the committee's statement that " a realistic estimate of likely expansion over the next few years " would reduce the average numbers on doctors' lists to those figures In the committee's view, 3500 persons on the list of a principal, plus 2000 where an assistant was employed, reflected the needs and conditions at the time when the committee met.

The Lancet · Saturday 1 October 1960

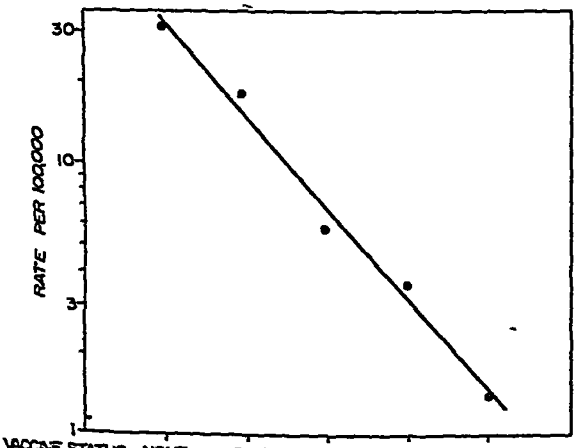
PERSISTENCE OF IMMUNITY AFTER ADMINISTRATION OF FORMALIN-TREATED POLIOVIRUS VACCINE *

JONAS E SALK
M.D New York Univ
DIRECTOR OF VIRUS RESEARCH LABORATORY AND COMMONWEALTH PROFESSOR OF EXPERIMENTAL MEDICINE AT THE UNIVERSITY OF PITTSBURGH
From the School of Medicine, Pittsburgh, Pennsylvania

A PROPER appreciation of the question of persistence of immunity following administration of a formalin-treated poliovirus vaccine requires an understanding of the factors that influence the initiation of immunity

Initiation of Immunity

An interesting approach is afforded by experience in the United States in 1959, when cases of paralytic poliomyelitis were sufficiently widespread and numerous to permit comparison of the relative efficacy of different numbers of doses



VACCINE STATUS	NONE	ONE	TWO	THREE	FOUR	Doses
Estm. Population (millions)	47	1.3	3.6	74	3.6	
Number of Cases	1508	234	209	267	51	
Rate/100,000	321	18.0	58	3.6	14	

Fig 1—1959 paralysis-rate in age-group 0–4 years

NUMBER OF INJECTIONS

During the year, 5267 cases of poliomyelitis with residual paralysis were recorded (Langmuir 1960) Of these, 2269 were in the age-group 0–4 years, and their vaccination status was as shown in fig 1 This reveals an inverse linear relationship between the paralysis-rate (plotted on a logarithmic scale) and the number of doses administered at unspecified times

Fig 2, containing similar data for the age-groups 5–19 and 20–39, shows a reasonably good alignment of points for those receiving one or more doses of vaccine For the unvaccinated in these age-groups, however, the non-alignment of the points suggests the possible operation of the factors revealed by Francis in the 1954 field trial, in which the incidence of poliomyelitis was lower in the observed-controls than in the placebo-controls (Francis et al. 1957) As in that trial, a lower socioeconomic status might account for a lower-than-expected relative incidence of paralytic poliomyelitis in the unvaccinated In the 0–4 age-group (fig 2) the approximation of all of the observed points to a straight line suggests that, in the early years of life in the United States, susceptibility is more uniform, and less affected by status The data from which figs 1 and 2 were constructed are given in the table Reasons for non-alignment of the lowest point for the 20–39 age-group come to mind, but the number of cases is too small for useful comment.

Type-1 virus was identified in 89 5% of the 3910 cases in which poliovirus was isolated (Langmuir 1960) Type-3 virus was found in 10 1% and type-2 virus in 0 4% In view of this preponderance of type-1 virus, the overall effect of vaccination revealed in figs 1 and 2 may be considered to reflect principally the efficacy of the type-1 component of vaccine used during the period in question

It is clear from fig 1 that in part of the vaccinated population even a single dose of vaccine conferred immunity The linear relationship indicates that each successive dose reduced the remainder of the susceptibles by the same proportion as did the first dose If this example represents a general rule for vaccines that induce immune conversion in only a proportion of those vaccinated, its significance can be further appreciated by examining a series of hypothetical curves describing the cumulative percent conversions assumed to take place after successive doses of vaccines of different one-dose conversion efficiencies This is illustrated in fig 3, where the cumulative percent conversion is plotted in relation to number of doses The 1959 paralysis-rate data from fig 1, converted to percent effectiveness, are also plotted in fig 3 Their relation to the hypothetical curves indicates

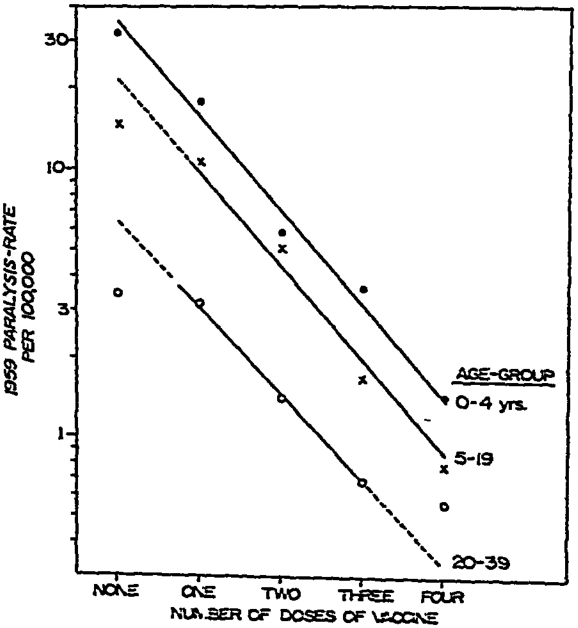


Fig 2—Paralysis-rate according to vaccination status.

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* Presented in part at the Fifth International Poliomyelitis Conference, Copenhagen, on July 27, 1960

NUMBER OF CASES AND PARALYSIS-RATE ACCORDING TO VACCINATION STATUS IN UNITED STATES IN 1959

Age-group and vaccination status	Estimated * population September, 1959 (thousands)	Paralytic poliomyelitis †	
		Number of cases	Rate per 100,000
0–4			
0	4700	1508	32 09
1	1300	234	18 00
2	3600	209	5 81
3	7400	267	3 61
4+	3600	51	1 42
Total	20,600	2269	11 01
5–19			
0	6800	997	14 66
1	1500	159	10 60
2	3900	198	5 08
3	23,300	390	1 67
4+	12,600	99	0 79
Total	48,100	1843	3 83
20–39			
0	22,800	787	3 45
1	2000	64	3 20
2	4800	67	1 40
3	12,400	86	0 69
4+	4600	26	0 57
Total	46,600	1030	2 21

* Based on random survey of 17,500 families, Census Bureau, September 1959

† Final report corrected for 60-day follow-up

Source U S Public Health Service, poliomyelitis surveillance report no 197, May 16, 1960

that, in 1959, the average effect for a single dose was more than 50% The curves for vaccines of low potency suggest that, with progressive decline in one-dose effect, multiple doses of weak vaccine become less and less efficient for immunisation Conversely, the greatest efficiency is associated with vaccines that approximate a full effect after one dose

Fig 4 shows the data for 1959, plotted logarithmically, along with illustrations of hypothetical cumulative immune-conversions assumed for vaccines that induce 60, 75, or 90% conversion after a single dose It illustrates somewhat more pointedly than fig 3 the diminishing returns of successive doses of relatively weak vaccine, and the greater efficiency of more potent vaccine Like fig 1, it also shows that the cumulative increase in immunes is augmented after each dose as though those who did not respond initially do respond to later doses—with the same probability of conversion as if they were being treated for the first time with vaccine of that potency These relationships suggest that immunity results from the first effective antigenic stimulus, and that, if the first dose does not induce immunity, a critical level may be reached after subsequent doses They also suggest that, if a critical level of response can be achieved after one injection, then uniform immunisation by one dose of a killed-virus vaccine is theoretically possible

In considering how far paralytic poliomyelitis occurring in triply vaccinated people is due to failure to induce an immune response initially, and how far it is due to waning immunity, it is helpful to examine more closely the relationships illustrated in fig 4 Clearly, with each additional dose a greater proportion of the vaccinated population was protected, protection reaching about 92% after three doses and about 96% after four If the dosage-response line, as drawn in fig 4, is projected, a fifth dose should increase the proportion of immunes by approximately 2%, and a sixth would add a further 1%, still leaving about 1% unprotected The use, for any dose, of vaccines of 75% or 90% conversion-efficiency in one dose would cause more vertical deflections as shown by the hypothetical projections after the fourth dose The diminishing return of successive doses emphasises the desirability of achieving the highest level of immunisation with the fewest injections

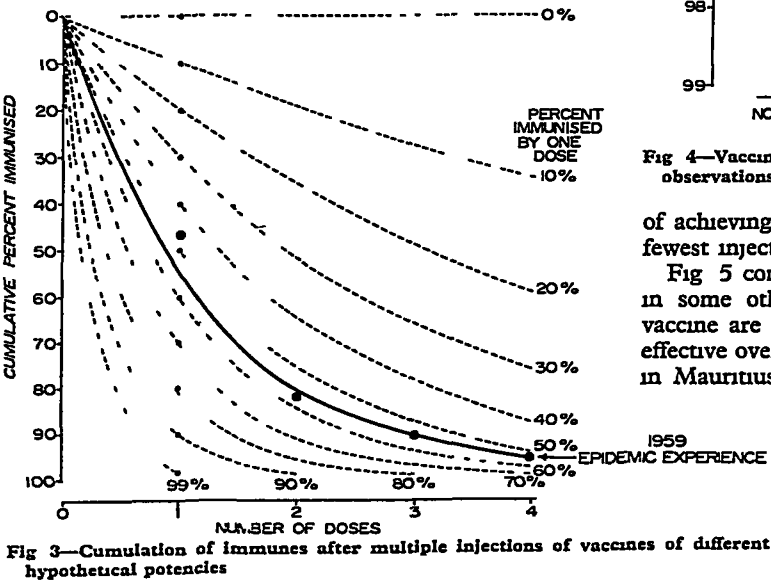


Fig 3—Cumulation of immunes after multiple injections of vaccines of different hypothetical potencies

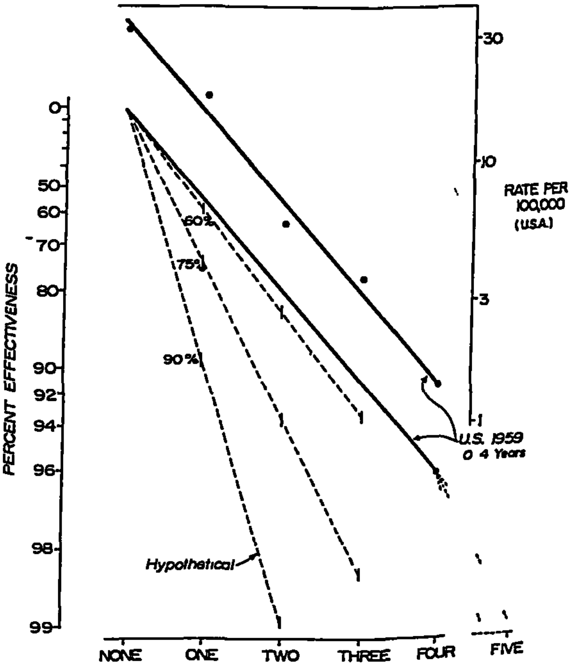


Fig 4—Vaccines of different hypothetical potencies compared with observations in 0–4 age-groups

Fig 5 compares experience in the United States and in some other countries In Belgium three doses of vaccine are estimated to have been approximately 95% effective over a two-year period (Prinzie et al 1960), and in Mauritius a single severe outbreak revealed approximately 99% protection by three doses (Poliomyelitis Surveillance Unit 1960) The probable one-dose effects of the average of the vaccine used in these areas may be deduced from this graph In Sweden, Olin (1960) has reported 97% effectiveness for three doses—the first two largely

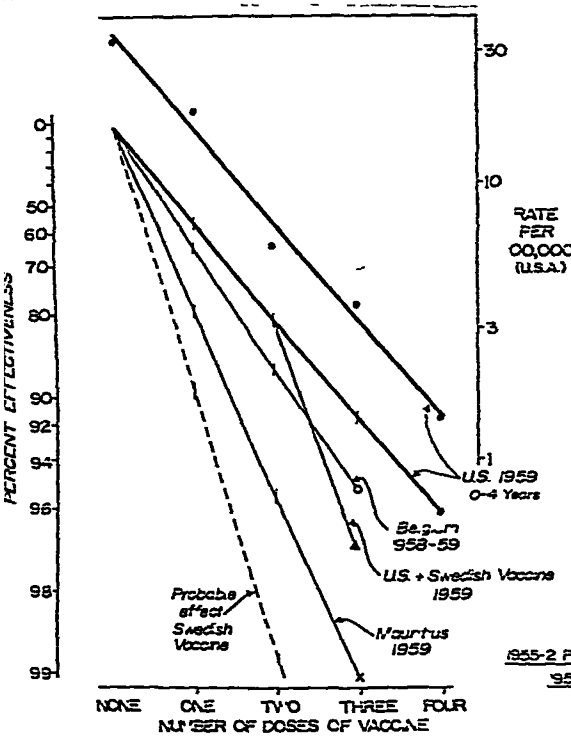


Fig 5—Comparison of effectiveness in selected instances.

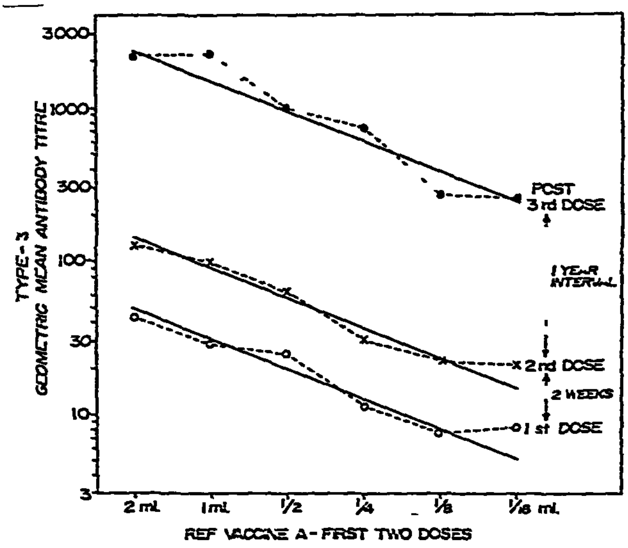


Fig 6—Dosage response effect. Type-3 antibody levels 2 weeks after each dose.

from United States sources and the third made in Sweden. If the effect of the first two doses of vaccine used in Sweden was the same as the average effect of vaccine used in the United States, Swedish vaccine used for the third dose can be interpreted as having been approximately 85–90% effective in a single dose (as suggested by a line from the 0-point and parallel to the line drawn between the second-dose and the third-dose points) If the average potency of American vaccine used in Sweden was greater than the overall United States average, then 97% protection could have followed the third dose even if the Swedish vaccine had been of somewhat lesser potency These examples indicate the possible usefulness of this kind of analysis

The relationships shown in figs 4 and 5 suggest that the use of vaccines of greater conversion efficiency would considerably reduce vaccine failures Moreover, the linear relationship between dose and immunising effect is not incompatible with the possibility that the effects are irreversible If this is so, it would seem that long-term immunity can be induced by a single adequate antigenic stimulus

ANTIGENIC MASS

In immunisation with a formalin-treated virus vaccine, the use of multiple injections is based partly on the knowledge that high levels of antibody can be induced by a smaller dose of antigen if that dose is divided instead of being given on a single occasion. As shown in fig 6, using reference vaccine “A” in man, when two doses were given, only about half as much antigen was required,

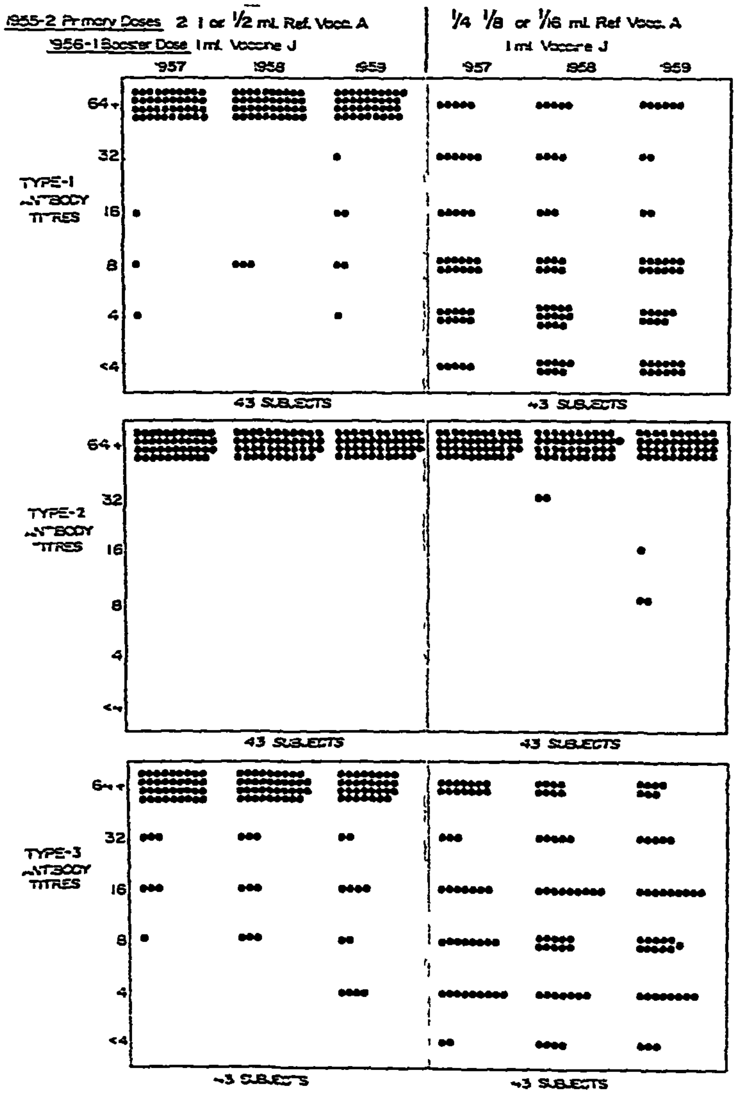
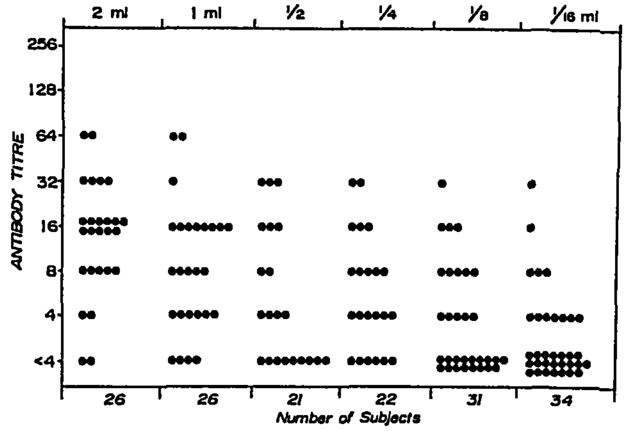
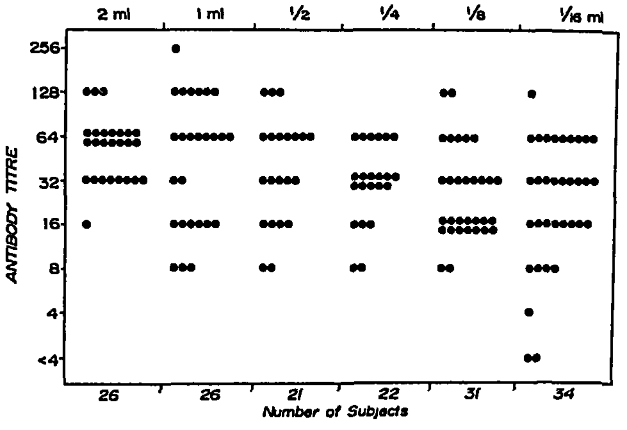


Fig 7—Types 1, 2, and 3 antibody titres up to 3 years after booster dose.

to reach an equivalent antibody level, as was required when a single dose was given When a third dose, which was uniform for all six groups, was postponed until one year later, substantial increases in antibody levels occurred—far beyond that induced by a single dose of a much larger amount of antigen While the striking effect of a third dose given one year later is as shown in fig 6, it was found that a third dose given only two weeks after the second induced only slight changes in titre, which shows the need for adequate spacing of doses if the maximal response is to be obtained from small amounts of antigen



Reference Vaccine A- 2 doses 2 weeks apart



Reference Vaccine A- 2 doses 2 weeks apart

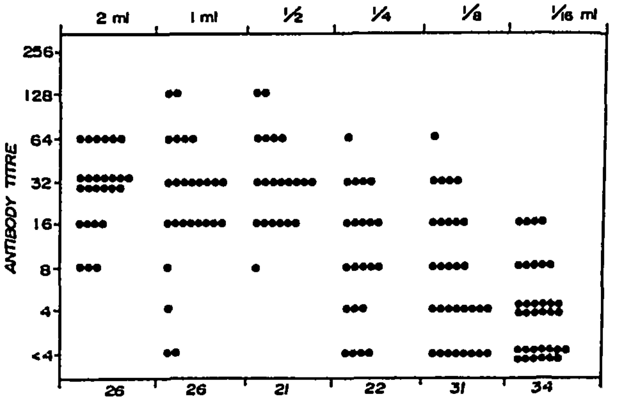


Fig 8—Types 1, 2, and 3 antibody titres 1 year after primary vaccination

The top, middle, and bottom portions of the figure refer to data for types 1, 2, and 3 respectively

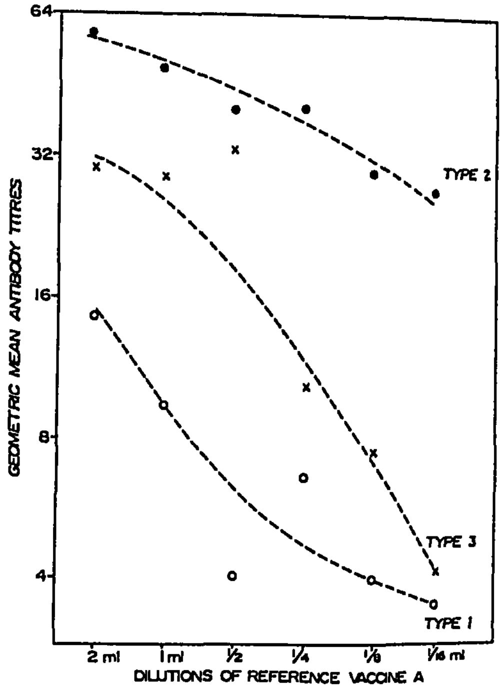


Fig 9—Dosage response effect Geometric-mean antibody titres 1 year after primary vaccination (two doses, 2 weeks apart)

The high antibody levels developed after the booster dose are not required for induction of the immune state, effective immunity to paralysis can be induced by a primary antigenic stimulus

Persistence of Immunity

ANTIGENIC MASS

Antigenic mass affects not only the level of antibody developed initially but also the persistence of demonstrable antibody At one year and two years after a booster dose, higher levels of antibody, and a higher proportion with demonstrable antibody, are found in groups given a larger dose for primary immunisation (Salk 1958) In the experiment illustrated in figs 6 and 7, the levels of antibody, and the proportion with demonstrable antibody, were higher in those who had been given the three larger doses of vaccine than in those given the three smaller doses Since the booster doses were the same, the level of antibody persisting was evidently related to the mass antigen employed for the initial injections It appears from these data (fig 7) that successful induction of a state wherein antibody formation tends to persist, and the level at which this is maintained, are linked to the amount of antigen in the initial dose of vaccine

If the level of antibody one year after the booster dose were found to be related to the subsequent level of persistence, this might also be true of the level of antibody one year after primary immunisation Fig 8 shows, for each of the three types, the distribution of antibody levels one year after two doses, given two weeks apart, of different dilutions of reference vaccine "A" Clearly the frequency with which antibody is present one year after primary vaccination is determined by the mass of antigen employed Moreover, as is to be expected, the mean level of antibody is correspondingly influenced

When geometric-mean antibody levels for each type are plotted (fig 9) in relation to quantity of reference vaccine "A" used for immunisation, the results arrange hemselves at different levels and along lines of different hape The meaning of the different levels and lines of ifferent shape could be that each was but a segment of a nore extensive curve, and not part of a straight line escribing a simple function The reasonableness of this xplanation became apparent when the lines were earranged by horizontal shifting so as to touch at ssentially overlapping points When this was done (fig 10) he points approximated a single sigmoid curve This uggests that if the titration series could have been xtended to the same limits for each type, a similar igmoid curve would have described the dosage-response ffect in each instance The meaning of the shape of this urve will be discussed at a later time

The quantitative relationship shown in fig 10 is of particular interest at present since it suggests the nature and extent of decreases or increases in antigen content, in relation to reference vaccine " A ", that may be permitted, or may be required, to achieve an equally high level of performance for all three types By plotting (fig 11) the percentage of persons with antibody titres of 1/4 or more one year after vaccination, in relation to the abscissa used in fig 10, it becomes apparent that there is a critical antigen content below which this percentage falls sharply

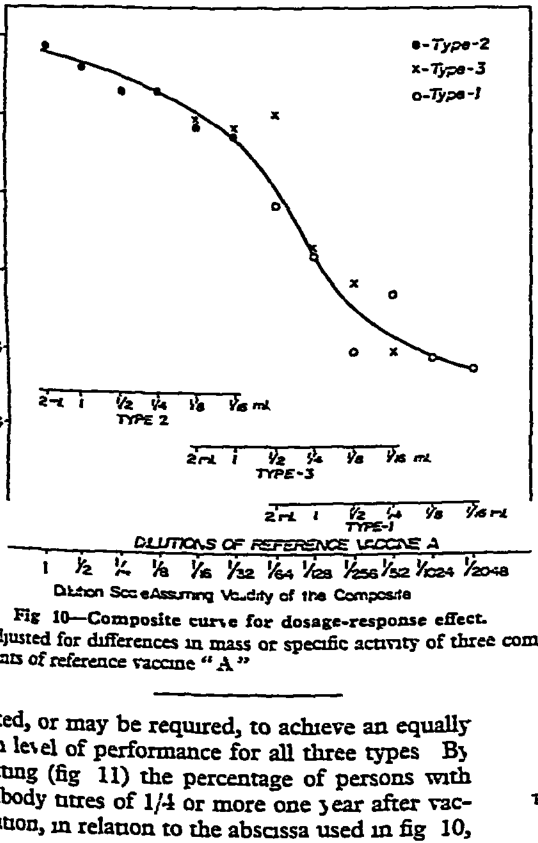


Fig 10—Composite curve for dosage-response effect.

Adjusted for differences in mass or specific activity of three components of reference vaccine " A "

If the object of immunisation is to achieve a level of antibody that persists for at least a year after primary vaccination, the relationships shown in fig 11 (left-hand curve) indicate the approximate relative amounts of the respective antigens contained in reference vaccine " A " that may be expected to attain this objective, when two doses are given two weeks apart Fig 11 also shows (right-hand curve), for comparison, the one-dose response measured at two weeks

Although levels of potency based upon positive serological criteria would be higher than levels based upon paralysis-prevention criteria, a good estimate of the requirements for optimal potency can be deduced, in part, from the relationships revealed by the data presented in fig 4 The assumption may be made that the immunising effect for type 1 should be increased to the extent desired beyond that of approximating a 50% effect with a single dose The amount of antigen needed for such an increase may be deduced from the relationships shown in fig 11, which indicates that the amount of type-1 antigen contained in one dose of 1/2 dilution of reference vaccine ' A " was sufficient to induce, in all subjects, titres of 1/4 or more after one dose, and that, after a two-dose primary vaccination, about four times this amount was necessary to induce a demonstrably persistent level of antibody for one year From fig 7 it seems that when primary vaccination

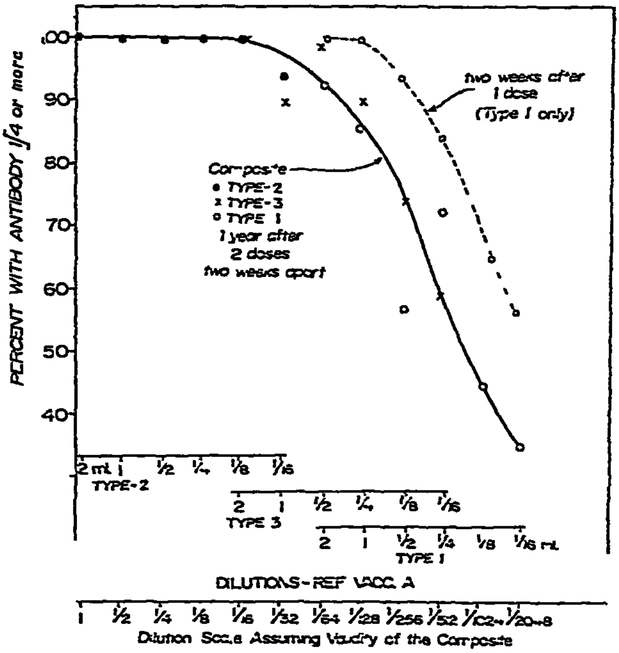


Fig 11—Composite curve showing percent with antibody at level of 1/4 or more

Derived from dosage response data adjusted for differences in mass or specific activity of three components of reference vaccine " A "

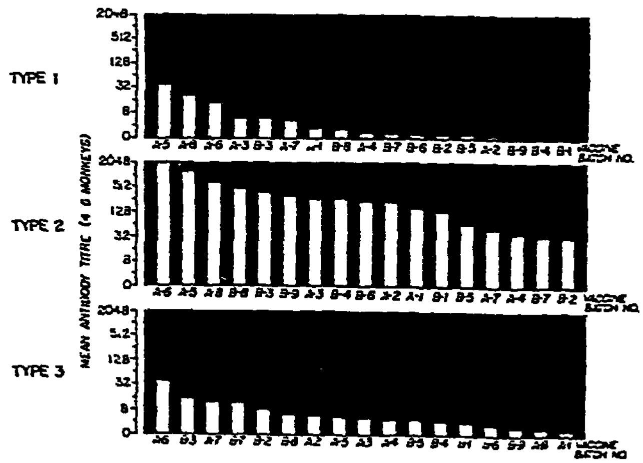


Fig 12—Mean titre of antibody in cynomolgus monkeys 4 weeks after a single administration of 10 ml. of 18 different batches of poliomyelitis vaccine divided among four intramuscular sites. (From Salk et al. 1955)

consisted of two doses of a 1/2 dilution of reference vaccine " A " given two weeks apart, followed by a third dose a year later, antibody was still demonstrable for at least another three years

If the relationships thus revealed in terms of antibody are true also of immunity to paralysis, it would seem that an antigen content increased eight-fold to ten-fold over the average of the recent past is in the range of the minimum required for optimal effectiveness for type 1 This estimate is in the range found by Barnett and Baron (1960) to compensate for deficiencies in potency They, and Dane et al (1960), recommend that in the face of epidemics, 10 ml of the generally available vaccine should be used to obtain prompt and more uniform effects—comparable to those induced by 1 ml of reference vaccine " A "

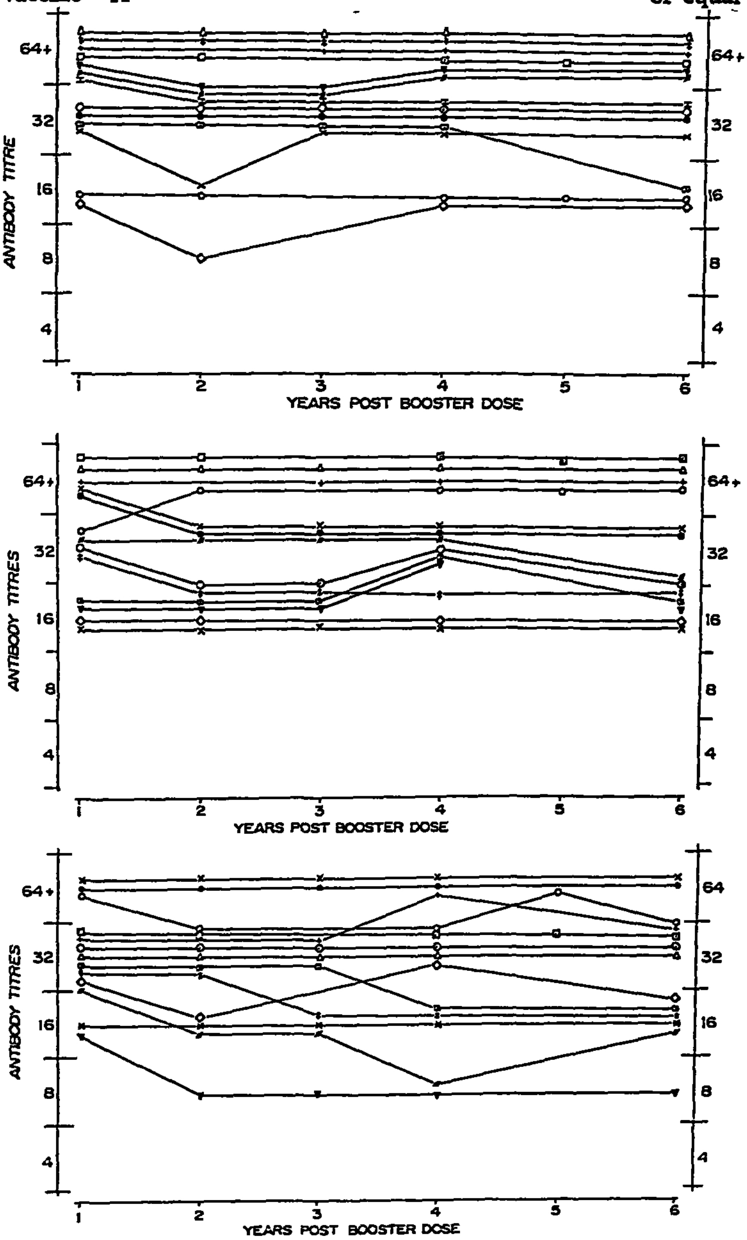


Fig 13—Types 1, 2, and 3 antibody levels at 1 to 6 years after booster dose in triple-negative children.

The top, middle, and bottom portions of the figure refer to data for types 1, 2, and 3 respectively

Two doses 2 weeks apart, third dose 7 months to 1 year later

Although these analyses indicate an increase in the average amount of type-1 antigen, the problem may be more simply one of assuring stability and restricting acceptability only to lots of vaccine of such potency as can be expected to perform as intended These analyses also suggest that the amount of type-2 antigen may be reduced. Specifications for type 3 should be determined, using as a guide field experience for type 1 and the immunological experience with the type-3 component of reference-vaccine " A "

ANTIGENIC CAPACITY OF DIFFERENT STRAINS

Apart from quantity, account must be taken of the intrinsic capacity of the antigen to induce an immune reaction Though reference vaccine " A " was comprised of equal parts of culture fluid containing virus of each type, converted to vaccine in essentially the same manner, the response to type 2 (MEF-1) differs from the response to the other two components (figs 7, 9, and 10) This difference is unlikely to be due only to differences in quantity or mass of antigen that some qualitative difference must exist has long been appreciated (Salk et al 1953, Salk et al 1955) Because of the potential importance of the difference in antigenic capacity among these strains (Mahoney, MEF-1, and Saukett), an investigation is under way exploiting the earlier observed difference (Salk et al 1955) in one-dose response in monkeys (fig 12) Although multiple injections obliterate the marked one-dose difference by enhancement of response to all three strains, the possibility of differences in degree and persistence of immunologic response to different strains of virus is interesting both theoretically and practically

PROJECTION OF ANTIBODY PERSISTENCE

Fig 7 illustrated the degree of persistence of antibody during the three years following the last dose of vaccine The trends over a period of about six years, following a booster dose given seven to twelve months after primary immunisation, are shown in fig 13 These data show that the level of demonstrable antibody a year after the booster dose is a guide to the level during the next six years The individuals comprising the group shown in fig 13 were among those in whom good response occurred They appear to follow the pattern of the group given the larger dose of reference vaccine " A " for primary immunisation (fig 7) The persistence of antibody after primary immunisation (fig 14) is similar to that following the booster dose Instances of a rise in antibody titre for one type (indicative of natural infection during the period of observation), or for two or three types (suggesting vaccination), have been excluded from the foregoing analyses The present observations bear on the unresolved question whether persistence of antibody to a virus disease requires either the continued presence of living virus or repeated reinfections They suggest that antibody can persist merely as a result of an initially adequate antigenic stimulus

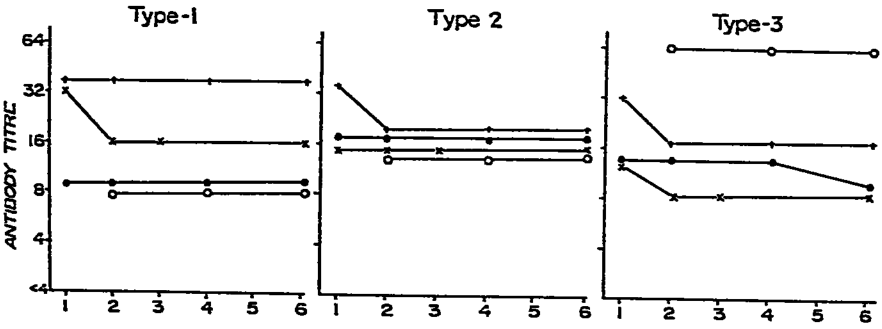


Fig 14—Antibody levels at 1–6 years after primary vaccination in triple-negative children. Three doses 2 weeks apart. (Field trial vaccine, 1954.)

From figs 13 and 14 as well as fig 7, it seems that for predicting the decline in antibody level with time, a line connecting the levels one year and two years after the booster dose will be more informative than the line connecting the levels two weeks after primary vaccination and one year after the booster dose. The pattern of the two different projections can be seen from fig 15, which shows antibody levels over a seven-year period in a child given one primary and one booster dose seven months apart. A similar pattern of persistence in the early and later periods has been observed after primary immunisation.

Whether a persistently demonstrable level of antibody is essential for persistently effective immunity to paralysis is not certain, since there is reason to believe that immunity to paralysis continues in those rendered immunologically hyperreactive by contact with antigen, and in whom antibody may no longer be detectable by usual methods (Salk 1956b). But there can be no doubt that for maintaining a readily demonstrable level of antibody the intensity of the initial antigenic stimulus is important.

Is Induced Immunity Reversible?

The idea suggested earlier that a single dose of antigen may have an irreversible immunising effect looks more plausible in the light of the evidence presented above.

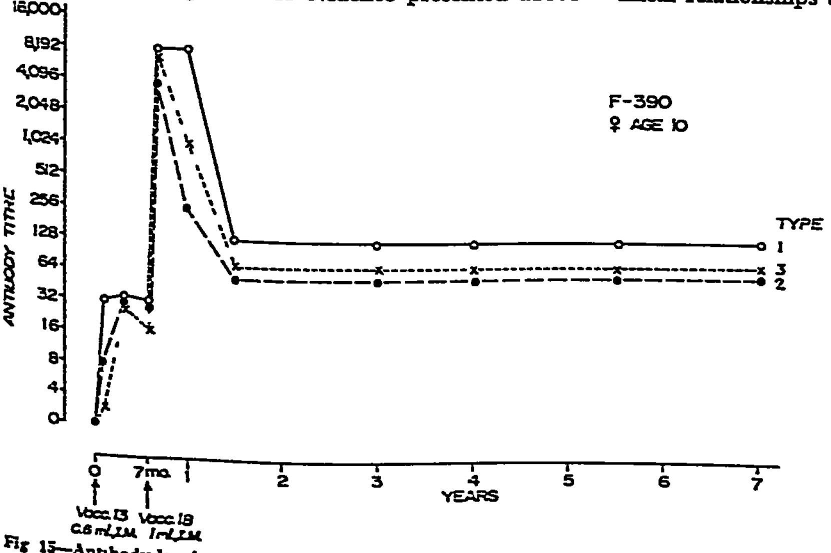


Fig 15—Antibody levels over a 7-year period in a child given two doses, 7 months apart.

The importance of this idea for non-infectious vaccines in general, warrants examination of the dynamics that might be involved.

Ordinarily vaccination is regarded as adding to the host something that was not there before—i.e., a state of immunity. But there is another possible way of looking upon this phenomenon—an alternative explanation of the effects of vaccination—namely, that it inactivates susceptibility. This may lead to another way of thinking about the dynamics of immunisation.

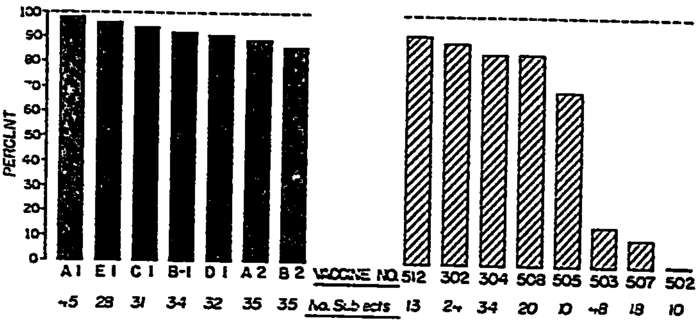


Fig 16—Percentage of children with antibody response type 1 on the 14th day after first dose of vaccine. (From Salk 1955.)
No prior demonstrable antibody to any type.

If the hypothesis that long-term immunity can be induced by a single antigenic stimulus is correct, we might then speak not only of vaccination inactivating susceptibility but also perhaps of an irreversible inactivation of susceptibility comparable to the inactivation of a virus. In line with this reasoning, the linear relationship in fig 1 brings to mind the dynamics of biological systems in which irreversible inactivation takes place. Such linear relationships usually imply that the inactivation of the measured property is a consequence of some single or final critical event. In this instance, the relationships in fig 4 suggest that the likelihood of the critical event is influenced by the mass of antigen employed. The nature of the critical event can be suggested only in the broadest terms, but it can be imagined as the conversion of a sufficient number of antibody-forming cells to a state in which, on exposure to natural infection, they will produce enough antibody to prevent paralysis.

The slope of the line describing the rate of inactivation of susceptibility becomes steeper with increasing concentrations of antigen in the vaccine (fig 4). This would be analogous to the increased rate at which virus is inactivated when one increases the concentration of formaldehyde or raises the temperature Just as a 1/8000 or a 1/16,000 concentration of formalin at 37°C would take an inordinately long time to inactivate poliovirus for vaccine preparation, so a vaccine with a concentration of antigen able to inactivate (by a single dose) the susceptibility of only 50–60% of subjects may take an inordinately large number of injections and an inordinately long time to have the desired effect

In using a formalin-treated virus antigen, therefore, the aim should be a preparation that is fully effective in a single dose Whether this is to be accomplished by sufficient concentration of the antigen or by the use of an adjuvant is a detail to be decided on other grounds The point of importance is that whatever increases the frequency of effectiveness will simultaneously enhance the durability of effect

Discussion

When the value of a preventive measure is demonstrated, the need to apply it soon destroys the chances of varying, in a controlled way, the critical factors on which more precise knowledge may be required For this reason, it was not expected that much further quantitative information on the efficacy of vaccination could be gathered beyond that derived from the Francis study (Francis et al 1957) However, valuable information on the incidence of paralytic poliomyelitis in relation to the number of doses of vaccine was collected in the United States in 1959 This was possible because of the excellence of the poliomyelitis surveillance programme of the United States Public Health Service, and the cooperation it receives from various agencies and professions

DYNAMICS OF IMMUNISATION

This 1959 experience provided an unusual opportunity for titrating vaccine effectiveness according to the number of doses, using immunity to paralysis rather than antibody level as the endpoint The degree of protection to be expected after successive doses proves to be related to the protection conferred by a single dose The 50% paralysis-protection endpoint for one dose has provided a basis for estimating the nature, direction, and extent of the changes required to approximate full effectiveness through adjustment of vaccine potency

It has been shown that when adequate antigenic stimulation is induced initially, antibody persists for at least six years, and even if immunity to paralysis continues after antibody has declined to non-measurable levels (Salk 1956b), it seems much more likely to continue where demonstrable antibody has persisted for a year or more than where it persisted only a few weeks or months Long-term presence of antibody has been induced by primary immunisation, and this encourages the hope that a single dose, if suitably adjusted in potency, may regularly have long-term and possibly even permanent effects

A one-dose procedure is the goal. Meanwhile, however, it should be possible at least to fulfil the original intention of giving full protection by means of two primary doses The present three-or-four-dose procedure still leaves a small but measurable residue of susceptibles but this remnant of the consequences of earlier imperfections could be dissolved by a single dose of vaccine of optimal potency

When a two-dose primary vaccination procedure was first proposed (Salk 1955), it was assumed that vaccines would approximate the antigenic potency of the 1954 field trial material prior to the deteriorating effect merthiolate The first seven batches of vaccine com mercially prepared in 1955 are compared in fig 1 (Salk 1955) with representative lots of field-trial vaccin it shows that after a single dose, at least 85% of thos vaccinated with the 1955 material developed an antibod titre of 1/4 or more whereas potency of some lots of th 1954 material, which had been impaired by merthiolat action, were of lesser effectiveness

It was to be expected that two doses of vaccines o such potency would have closely approximated fu effectiveness, and that a third dose, seven months to year later, would induce the high levels associated wit the booster phenomena These expectations wer fulfilled (Salk 1956a) However, a survey made in 195 showed that the vaccines then in general use were les effective (Salk 1959a)

The 1959 experience (fig 4) suggests that one dos protected an average of about 50%, three doses protecte about 92%, and four doses protected about 96% Th decrease in efficiency between 1955 and 1959 can b explained as due to use of a mixture of vaccines of hig and low potency (fig 16) From data in fig 11 it appears that the range of potencies of vaccine manufactured in the United States, with respect to types 1 and 3, must have been in the critical range between poor and satisfactory, as judged by their effectiveness using the number of injections originally intended. By a shift to higher levels of potency, effectiveness with greater consistency can be expected, and a higher proportion of vaccinated subjects will show persistence of demonstrable antibody

PROSPECTS

The fact that vaccine potency was high in 1955, declined for a time, and is now increasing again (Murray 1960), indicates that levels of performance can be raised when the need is clearly established The five years' experience accumulated since the 1954 field trial has provided better understanding of what needs to be done to approximate perfection in the use of a formalin-treated virus vaccine against poliomyelitis Moreover, how this can be done has become much clearer

For example, the uncertainty of effect in young infants attributable to a variable amount of maternal antibody is greatest with vaccines of borderline potency, and can be overcome by more potent antigens If the vaccine used was of one-dose effectiveness, such uncertainty could be further reduced by the simple expedient of giving a second dose after 6 months of age Alternatively, mothers can themselves be immunised, and the immunisation of the child can be left until he is 6 months old.

Another approach to the problem posed by the inhibiting action of maternal antibody was suggested by an observation made earlier that antigen contained in a water-in-oil emulsion appears to be protected from the neutralising effect of antibody The use of such an emulsion can be expected (*a*) to enhance antigenicity, (*b*) to require the use of less antigen, and (*c*) to permit admixture of several viral and other compatible antigens into a multivalent vaccine to be given to all new members of the population early in life Whether mineral-oil adjuvants will ultimately be used depends on many factors still under study The likelihood that, in time, many different purified and concentrated antigens will be available, considerably extends the possibility of their manipulation to provide the most practicable procedure.

The method developed by Charney et al (1957) for concentrating poliovirus shows the possibility of preparing vaccine of any desired level of potency, and vaccine preparation can be simplified in other ways The possibilities include selection or development of strains of higher specific antigenic activity, and the use of continuously propagating cells for cultivation of virus These possibilities justify the expectation that the objectives reached for poliomyelitis will be extended to include antigens for a number of other viral diseases

With vaccines of single-dose effectiveness, not only will almost all vaccinated people be protected promptly and persistently, but the spread of virus in the population will be dampened more efficiently, and even totally suppressed Prevention of spread of virus from the intestinal canal to the pharynx, by antibody in the bloodstream, would protect the community by reducing the pharyngeal reservoir (Salk 1959b) which in some parts of the world seems to be a more common source of spread than fæcal contamination There is reason to think that, where vaccination has been widespread, type-2 virus may already have been substantially suppressed (Salk 1959a) If this proves to be so, it may be due to the greater antigenic effectiveness of the vaccine for this type, and a similar herd effect may be expected for types 1 and 3 when immune conversion for these types reaches the type-2 level.

The statement sometimes made (Chumakov 1960), that 20 or 30% of the population are not protected by the formalin-treated virus vaccines at present available, does not seem to be in keeping with the observations reported or cited here If some people are totally non-responsive, they must be very few—i e , they have escaped notice in observations on more than 10,000 individuals There are, however, some who react more to one type than to the others These rare individuals are being accumulated, and in time more will be known about them and their frequency

Concluding Remarks

These studies on immunisation with formalin-treated virus antigens have had as their purpose, in part, the establishment of the parameters within which protection against poliomyelitis paralysis could be induced with a high degree of certainty The work was begun on the assumption that two or more doses of vaccine would always be required, but experience now suggests that lasting protection against the disease should be attainable with a single dose

The view that a formalin-treated virus vaccine for poliomyelitis was merely a stage awaiting the development of a live virus vaccine seems to have underestimated the potentialities of non-infectious viral antigens

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A TRIAL OF
CONTINUOUS WINTER CHEMOTHERAPY IN CHRONIC BRONCHITIS

RONALD B PRIDIE
M B Lond
LATELY MEDICAL REGISTRAR

NAOMI DATTA
M.D Lond., Dip Bact
ASSISTANT LECTURER IN BACTERIOLOGY

D G MASSEY
M.D Toronto
MEDICAL REGISTRAR

GRAHAM W POOLE
M B Birm , M R.C.P
ASSISTANT PHYSICIAN

J SCHNEEWEISS
M B Sydney
MEDICAL REGISTRAR

PETER STRADLING
M D Lond , M R C P
PHYSICIAN AND LECTURER

From the Hammersmith Chest Clinic and Postgraduate Medical School of London, W 12

THE death-rate from chronic bronchitis far exceeds that from cancer of the lung, and it is some five times that from road accidents (Ministry of Health 1958)

As the serious plight of patients with chronic bronchitis is increasingly recognised, the problem of relief is receiving widespread attention Waller and Lawther (1957) and Lawther (1958) showed that the wellbeing of chronic bronchitics varies inversely with the smoke concentration of the atmosphere, Oswald and Medvei (1955), and many others (Edwards et al 1959, Flick and Paton 1959, Higgins 1959) have shown a relation between smoking and chronic bronchitis Because these factors are beyond the direct control of the physician many workers have used chemotherapy in efforts to reduce the infection associated with the disease, and drugs have been given during exacerbations only or continuously during the winter months

Elmes et al. (1957), Moyes and Kalinowski (1959), and Berry et al. (1960) showed, in controlled trials, that treatment with oxytetracycline or tetracycline, 1 g daily, given only during exacerbations, might shorten the exacerbation and reduce considerably the time lost from work.

Helm et al. (1954, 1956) treated a small number of patients with continuous oxytetracycline (1–3 g daily), and reported improvement. May and Oswald (1956) made a similar claim for daily doses of tetracycline or oxytetracycline of 0 25–1 g

Controlled trials of continuous daily chemotherapy have been undertaken with chlortetracycline 0 5 g in 30 patients (McVay and Sprunt 1953), using various doses of oxytetracycline or ‘ Sulphatriad ’ in 53 patients (Edwards et al. 1957, Edwards and Fear 1958), using tetracycline 0 75 g in 90 patients (Moyes and Kershaw 1957), using tetracycline 0 5 g in 51 patients (Buchanan et al. 1958), using tetracycline 0 75 g in 25 patients (Moyes and Kalinowski 1959), and with a tetracycline-oleandomycin preparation 1 g in 23 patients, or oxytetracycline 1 g in 75 patients (Murdoch et al. 1959) All claimed benefit from the tetracycline group of drugs In the recent trial of chemotherapy in chronic bronchitis conducted by the British Tuberculosis Association (1960) both tetracycline (0 5 g daily) and phenoxymethylpenicillin (penicillin V, 624 mg daily) halved the length of exacerbations but did not affect their frequency

The bacteriology of the sputum of chronic bronchitics has been studied by a number of workers, including Mulder et al (1952), Stuart-Harris et al (1953), and May (1953, 1954) All found that *Streptococcus pneumoniæ* and *Hæmophilus influenzæ* were the most significant organisms, and they pointed out that penicillin is highly effective against *Str pneumoniæ* but less so against *H influenzæ*, whereas sulphonamides, which are effective against *Str pneumoniæ*, have little effect on *H influenzæ*

To test further the validity of the published conclusions on long-continued chemotherapy, and to give penicillin with sulphonamide a practical trial, we undertook a double-blind controlled experiment to compare oxytetracycline, a penicillin-sulphonamide combination, and a placebo We thought it possible that the penicillin-sulphonamide preparation, as well as being cheaper (£10 per patient for the doses used in this trial compared with £33 for oxytetracycline), might produce fewer side-effects, and thus, if similarly effective, might prove more suitable

Method

The trial was held during twenty-four weeks, from Nov 2, 1958, and only adult chronic bronchitics with some exertional dyspnœa were admitted During the previous three winters each had had at least one disabling respiratory illness with two months' cough and sputum Patients with active tuberculosis, proved bronchiectasis, carcinoma of the bronchus, or other chest disease were excluded

The oxytetracycline dosage (0 5 g daily) was the minimum found effective in previous controlled trials (McVay and Sprunt 1953, Buchanan et al 1958) The treatment chosen for comparison was potassium phenoxymethylpenicillin 500 mg with sulphadimidine 2 g, in combined tablets daily

151 patients were admitted to the trial and divided into six subgroups by a method based on random sampling numbers Two subgroups were given penicillin-sulphonamide tablets and one subgroup had dummies of similar appearance, two subgroups received oxytetracycline tablets and the last subgroup had similar dummies Both placebos contained lactose The division into six subgroups was necessary because the tablets looked different, by combining appropriate subgroups, we obtained a placebo group similar in size to each treatment group These three groups comprised 51 patients having placebos, 51 having oxytetracycline, and 49 having penicillin-sulphonamide

At a preliminary interview, the trial was carefully explained to each patient, the work status was recorded, a chest radiograph was taken, and the grade of dyspnœa was assessed. The vital capacity and the forced expiratory volume in the first second (F E V $_1$) were estimated These tests were repeated after three months and at the end of the trial

Each fortnight every patient was given a diary card on which to record his daily condition by a code letter A = better than usual, B = same as usual, C = worse than usual, D = much worse than usual

All the sputum produced in a period of twenty-four hours was collected from each patient before the start of the trial and every two weeks thereafter The volume was measured each time and the macroscopic appearance graded as watery, mucoid, or purulent From the specimens provided initially, after a month, and at the end of the trial, counts were made both of total bacterial content and of individual organisms

TABLE I—EXCLUSIONS FROM ANALYSIS

Exclusions	Placebo group	Oxytetracycline group	Penicillin sulphonamide group
Complete			
Toxic	0	3	4
Non-toxic	1	2	2
Partial			
Toxic	0	0	3
Non-toxic	7	6	5
Total due to toxicity	0	3	7
Total no of exclusions	8	11	14

The patients were given postcards by which to notify the clinic of any respiratory illness, whereupon they were visited by a clinic doctor General practitioners were fully informed of the trial, and they were asked to discontinue the trial tablets during an exacerbation, and to give their customary treatment for acute bronchitis Both they and the patients were asked to ensure that the trial tablets were resumed afterwards All other usual supportive measures, such as bronchodilators, were continued as necessary throughout the trial

Daily records of the smoke and sulphur-dioxide content of the atmosphere were obtained from meteorological centres in three adjacent boroughs

Health visitors called fortnightly at the patients' homes to provide a coordinating influence on the trial and to encourage cooperation They exchanged the diary cards and ensured their completion, collected the sputum specimens, and issued further supplies of tablets, and collected those unused. (We thought this would give some indication of whether the patients had taken their tablets conscientiously Every fortnight patients were given a sixteen-day supply of tablets, and since it was the routine to return two days' tablets, we thought it likely that they would also unwittingly return any other tablets that should have been taken rather than throw them away)

At the end of the trial each patient's opinion was asked on the value of the treatment prescribed

Exclusions from the Analysis

Patients who failed to complete the first month of the trial were excluded entirely from the analysis (complete exclusion) Those withdrawn after one month were included in the analysis up to the time of their withdrawal (partial exclusion) The details are presented in table I

12 patients were completely excluded—1 in the placebo group, 5 in the oxytetracycline group, and 6 in the penicillin sulphonamide group This was because of intolerance to the drug in 3 patients on oxytetracycline (diarrhœa in each case) and in 4 on penicillin-sulphonamide (1 rash, and 3 complaints of dizziness)

The partial exclusions totalled 21, and in only 3 cases was drug intolerance the cause Factors such as lengthy admission to hospital or moving from the district were responsible for all

TABLE II—AGE AND SEX DISTRIBUTION (AFTER EXCLUSIONS)

Age (yr) and sex	Placebo group	Oxytetracycline group	Penicillin-sulphonamide group
20–29	4	0	1
30–39	2	2	1
40–49	10	5	4
50–59	16	15	13
60–69	16	17	19
70 +	2	7	5
All ages	50	46	43
All ages			
Male	37	34	36
Female	13	12	7
50–69			
Male	24	25	25
Female	8	7	7

the partial withdrawals in the placebo and oxytetracycline groups, and for 5 of those in the penicillin-sulphonamide group The others were due to abdominal pain in 2 patients and to giddiness in 1

Toxic reactions were more frequent in the penicillin-sulphonamide group than in the oxytetracycline group (7 to 3)

After exclusions there remain for analysis 50 patients in the placebo group, 46 having oxytetracycline, and 43 having penicillin-sulphonamide

Despite randomisation rather more young people were found in the placebo group than in the two treatment groups (table II), perhaps explaining the apparent initial differences favouring the controls (table III) This discrepancy may be due partly to the bigger number and greater ages of the exclusions from the treatment groups To evaluate this difference, the results for patients aged 50–69 were analysed separately Between these ages the three groups were more clearly alike in all aspects of their condition on admission to the trial. Both sets of figures are presented, and their similarity suggests that conclusions drawn from the whole series are valid.

TABLE III—CONDITION AT START OF TRIAL

	All patients			Age 50–69		
—	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide
Total patients	50	46	43	32	32	32
Sputum character						
No sputum	2	2	0	1	2	0
Watery	8	9	8	6	7	6
Mucoid	13	9	10	8	7	8
Purulent	27	26	25	17	16	18
Sputum volume (ml. per 24 hr)						
None	2	2	0	1	2	0
1–49	38	26	32	23	17	24
50 and over	10	18	11	8	13	8
Average	33 2	45 3	38 7	38 1	42 8	37 4
Vital capacity (litres)						
Under 1 5	2	5	4	2	2	3
1·5–2 49	19	18	17	14	15	13
2 5–3 49	23	20	16	16	13	11
3·5 and over	6	3	4	0	2	3
Average	2 70	2 38	2 39	2 45	2 38	2 41
F.E V$_1$ (litres)						
Under 1	16	20	17	12	14	12
1–1 99	20	24	17	17	17	14
2 and over	14	2	7	3	1	4
Average	1 44	1 08	1 21	1 19	1 08	1 24
Dyspnœa						
Slight	20	13	15	10	9	12
Moderate	21	19	19	14	15	14
Marked	7	10	7	7	6	5
Very marked	2	3	2	1	1	1
Activity						
Working	42	30	29	27	23	23
Not working	7	8	10	4	5	6
Housebound	1	6	2	1	4	1
Bedfast	0	0	0	0	0	0

The grade of dyspnœa for 1 patient and of activity for 2 patients on oxytetracycline were not available. For 2 patients on penicillin-sulphonamide no pulmonary ventilatory tests were done and the grade of activity was not available. All these patients were aged 50–69

Results

Sputum

Table IV shows a similar reduction in sputum volumes in all three groups in the last two months of the trial (March and April), when the weather was improving During the first four months, sputum volumes were reduced in the penicillin-sulphonamide group but not in the others There was no significant difference in purulence (at the 5% level, as used throughout this study) between the three groups at any stage of the trial

TABLE IV—MEAN SPUTUM VOLUMES (ml PER 24 HR)

Months after starting	All patients			Patients aged 50–69		
	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide	Placebo	Oxy-tetra-cycline	Peni-cillin-culphon-amide
0 (October)	33 2	45 3	38 7	38 1	42 8	37 4
1 (November)	36 5	45 7	34 0	45 3	46 5	30 4
2 (December)	38 2	45 9	37 9	41 1	48 9	36 6
3 (January)	35 8	46 1	33 6	37 4	47 9	27 1
4 (February)	35 8	44 5	30 5	43 5	47 3	27 9
5 (March)	28 6	35 5	27 3	32 7	31 8	24 9
6 (April)	23 7	30 4	24 4	26 0	30 1	21 6

Ventilatory Function

Only changes of 10% or more from the initial values were considered of clinical significance in assessing ventilatory function by standard methods Table V, compiled on this basis, reveals no significant difference between the groups, although the treated groups have a marginal advantage in relation to F E V$_1$, which is less obvious in the 50–69 age-group

Subjective Assessment

In the patients' subjective assessment at the end of the trial the proportion of patients noting benefit was similar in the placebo group and in the treatment groups There is no significant difference between the three groups in the proportion showing reduction of dyspnœa or change in exercise level

Figures derived from the daily recordings on the diary cards * show that the penicillin-sulphonamide group regularly did best, and the oxytetracycline group worst, although the difference reached statistical significance only in the second and fifth months The degree of improvement was calculated by scoring "better than usual" as 1, "same as usual" as 0, "worse than usual" as −1, and "much worse than usual" as −2 The indices so obtained were plotted on the same time-scale as the average figures for smoke concentration (see figure) As the sulphur-dioxide figures ran parallel with those for smoke, they are not reproduced. The graphs for each

TABLE V—CHANGES OF 10% OR MORE IN VENTILATORY FUNCTION

Ventilatory function	All patients			Patients aged 50–69		
	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide	Placebo	Oxy-tetra-cycline	Peni-cillin-sulphon-amide
Vital capacity (litres)						
October to January						
Increase	6	5	6	5	3	4
No change	30	18	17	21	13	12
Decrease	10	20	11	4	16	9
Total	46	43	34	30	32	25
October to April						
Increase	4	10	8	4	6	7
No change	25	17	14	16	13	9
Decrease	12	12	9	6	9	7
Total	41	39	31	26	28	23
F.E V$_1$ (litres)						
October to January						
Increase	9	7	6	6	6	2
No change	20	16	13	14	11	9
Decrease	17	20	15	10	15	14
Total	46	43	34	30	32	25
October to April						
Increase	6	9	7	3	7	4
No change	15	18	11	11	12	9
Decrease	20	12	13	12	9	10
Total	41	39	31	26	28	23

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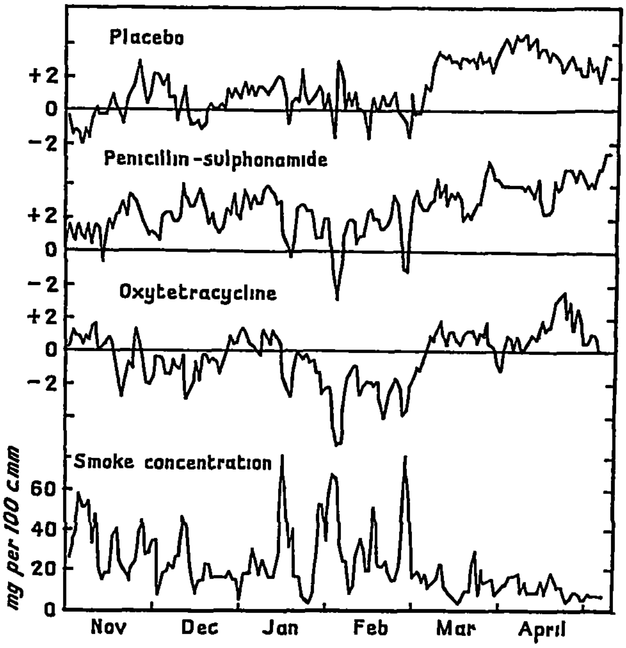
* Multigraphed tables of these figures may be had from *The Lancet*, 7, Adam Street, London, W C 2



Degree of wellbeing of patients in each group, and smoke concentration in the atmosphere

group all follow the same general pattern, and neither treatment altered their form The penicillin-sulphonamide graph is at the highest level (most improvement), the placebo graph is intermediate, and that for oxytetracycline is lowest

The trend in favour of penicillin-sulphonamide thus revealed may be important, although not statistically significant

Exacerbations

Some of the patients listed in table III as " working " were housewives in whom it was impossible to determine, by means of the number of days off work, the duration of disability in each exacerbation Accordingly comparison of such disability is only presented in relation to men (table VI) It is difficult to draw sound conclusions from the number of days off work per exacerbation because the trial tablets were stopped and the treatment was at the discretion of the general practitioners, but the patients in the treated groups were off work for a shorter time, on average, than those in the placebo group, although the differences were not statistically significant Table VI also shows a slight difference in favour of the treated groups in relation to the number of exacerbations

TABLE VI—EXACERBATIONS AND TIME OFF WORK IN MALE WORKERS

—	All ages			Aged 50–69		
	Placebo	Oxytetracycline	Penicillin-sulphonamide	Placebo	Oxytetracycline	Penicillin-sulphonamide
Total patients	32	25	25	21	21	19
No without exacerbations	12	11	11	6	10	8
No with exacerbations	20	14	14	15	11	11
No of exacerbations	29	28	24	23	25	16
No of days off work	430	271	309	351	261	249
Mean exacerbations per worker	0 9	1 1	1 0	1 1	1 2	1 2
Mean days off per worker	13 4	10 8	12 4	17 0	12 1	13 1
Mean days off per exacerbation	11 8	9 7	12 9	15 3	10 4	15 6

Bacteriology

Bacteriological counts * were recorded in logarithmic form because of the wide range of individual numbers No significant difference was shown between either of the treated groups and the control group in the total counts for any month Despite this the numbers of *Str pneumoniæ* were noticeably reduced in both treated groups, particularly after one month but also at six months, as compared with the placebo group Whilst the total bacterial counts were not raised, the incidence of *Str pneumoniæ* and *H influenzæ* was higher in the more purulent sputa, confirming the work of May (1953) Only 2 patients harboured staphylococci in their sputum at the end of the trial, neither strain was resistant to the drugs used The figures for *H influenzæ* were so variable that no trend can be detected

Tablet Taking

Only 10% of patients returned more than 10% of the tablets they should have taken Judged by this alone, cooperation in tablet taking seemed satisfactory

Discussion

This double-blind trial with 151 patients does not show clear benefit from long-continued daily administration of either oxytetracycline (0 5 g) or potassium phenoxymethylpenicillin (500 mg) with sulphadimidine (2 g) Our findings, like those of the recent trial (1960) conducted by the British Tuberculosis Association (B T A), do not confirm the substantial reduction in the *frequency* of exacerbations that McVay and Sprunt (1953) and Buchanan et al (1958) claimed with chlortetracycline or tetracycline 0 5 g daily On the other hand, neither of our treated groups showed so much reduction in the *length* of exacerbations as was obtained with tetracycline and with penicillin in the B T A trial (50%) A possible reason may be the different procedures followed during exacerbations, the B T A patients continued their prophylactic tablets whilst those in our trial did not Hence, the B T A patients probably had larger doses of antibiotics during exacerbations and consequently may have responded more quickly

As a reduction in sputum volume in the last two months of the trial was found in all groups, it was presumably independent of treatment and may have been due to the improving weather The penicillin-sulphonamide group, however, showed a steady and significant reduction in sputum volume during the first four months, and this group also had felt better Since these are the only two factors that stand out, the subjective improvement might be dependent upon the reduction in sputum volume Whether *continuous* administration of drugs is necessary to achieve this effect requires further investigation

In contrast to our findings a number of other workers have reported significant benefit from larger doses (0 75 g –1 0 g) of broadspectrum antibiotics Thus the dosage of the drug given may well be an important factor in producing a benefit Higher dosage, however, increases the cost and possibly the toxicity—factors which must be weighed against the possible benefits of giving long-continued chemotherapy to bronchitics generally

A correlation was noted between the rise in the smoke and sulphur-dioxide concentrations of the atmosphere and subjective deterioration in the patients confirming the work of Waller and Lawther (1957) This was so in all three groups, suggesting a dominant adverse influence of mospheric pollution on patients with bronchitis, which largely independent of chemotherapy

Some exacerbations are probably precipitated by the eather alone The therapeutic effect of the drug taken t the onset of such exacerbations may account for their horter length rather than the effect of the drug being uly prophylactic. If this is true, early and vigorous hemotherapy during exacerbations would be more logical han continuous administration

onclusions

The penicillin-sulphonamide combination was superior o both oxytetracycline and the placebo in reducing putum and increasing wellbeing of chronic bronchitics Nevertheless continuous daily treatment with oxytetracycline 0 5 g or with potassium phenoxymethylpenicillin 00 mg and sulphadimidine 2 0 g produced objective ffects so modest that we cannot recommend either egime The control of winter bronchitis may require ither a larger daily dosage of chemotherapy continuously, r very early and vigorous chemotherapy for exacerbations

Summary

151 patients with winter bronchitis took part in a louble-blind controlled therapeutic trial using a placebo, oxytetracycline, or a penicillin-sulphonamide preparation.

Daily doses of either oxytetracycline 0 5 g or potassium phenoxymethylpenicillin 500 mg with sulphadimidine 2 0 g was used The penicillin-sulphonamide group showed modest reduction of sputum volume and subjective improvement Both treatment regimes brought about a small reduction, not significant at the 5% level, in the length of exacerbations, and they also reduced the incidence and numbers of *Streptococcus pneumoniæ*, but not of *Hæmophilus influenzæ* A strong correlation was noted between atmospheric pollution and subjective deterioration of the patients, and this was similar in all groups

The findings suggest that neither therapeutic regime, at the continuous daily dosage here employed, can be recommended to control winter bronchitis

We are grateful to Dr C M Fletcher and Dr Philip Hugh-Jones or helpful criticism and for allowing us to include some of their patients, to Dr Ian Sutherland for statistical advice and help, to Miss B J Kinsley for the arduous statistical analysis of the results and for much constructive criticism, to Miss Kathleen Reade, Mrs June Haas, Mrs Mary Greenwood, and Miss Yvonne Newton, the health visitors, for their cooperation, without which the trial would have been impossible, to Mrs Megan Wall for central co-ordination and collection of data, to Mrs Eileen Till for invaluable secretarial assistance, to Pfizer Ltd., for the oxytetracycline ('Terramycin') and dummy tablets, to Eli Lilly & Co, Ltd, for the penicillin sulphonamide preparation ('V-Cil-K Sulpha') with dummies, and for a generous grant to cover expenses, to the medical officers of health for the boroughs of Chiswick, Fulham, and Kensington for allowing us access to the figures relating to atmospheric pollution kindly supplied by the Warren Spring Laboratory, Department of Scientific and Industrial Research.

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MIDDLE-MENINGEAL HÆMORRHAGE

THE GENERAL SURGEON AND THE NEUROSURGEON

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There are still too many deaths from extradural hæmorrhage This article is intended firstly to review the clinical features which may help a general surgeon to make his plans, and secondly to contribute to the organisation and practice of surgical treatment which at present is often haphazard. Though a few cases of extradural hæmorrhage will always be lost because of extensive coincidental brain damage, the others could and should be saved To achieve this end there must be (1) watchfulness by the hospitals accepting head injuries, (2) liaison between those hospitals and neurosurgical centres, and (3) well-planned surgery

Diagnosis

The diagnostic features of extradural hæmorrhage are well known, and a fully developed syndrome with a typical history is usually referred for surgery The case causing hesitation in calling for help is the atypical one, with delayed or deepening coma, equal pupils, no hemiparesis, and no visible fracture radiographically, but the pupils occasionally do not keep faith, and a fine crack fracture may be invisible with X-rays The only constant feature, therefore, is *advancing coma*—whether delayed, interrupted, or progressive

The possible presentations are

1 Coma appears for the first time 15 minutes to 48 hours (rarely up to a week or more) after a head injury

2 Coma is immediate after the injury, but is interrupted by the classical lucid interval

3 Coma is immediate after the injury and becomes progressively deeper These cases present the greatest difficulty in diagnosis, for the majority are due to cerebral laceration and in few is life further endangered by a collection of extradural blood-clot. More rarely still is subdural fluid blood present in significant quantity

Assessment of Unconsciousness

To say that "the patient is comatose" conveys little to the clinician, but the statement that "the patient is comatose and responds to nothing but severely painful stimuli on any of his limbs" is useful All the limbs must be tested because coma cannot be judged by pinching a limb unless one knows, by comparison with the others, that it is not paralysed A superficial pinch, if necessary firm and prolonged, is a more reliable test than a pinprick Any resultant bruises are of no consequence

That slowing of the pulse-rate may signify rising intracranial pressure is common knowledge, but it is less well known that phasic respirations precede the classical

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Cheyne-Stokes pattern, and often go unnoticed because the breathing is not watched for a minute at a time

Sleep may be superimposed on pathological lethargy, and in such a case stimuli more violent than those expected to rouse a sleeping adult serve only to lighten the coma momentarily Underlying drowsiness can only be revealed by efforts to keep the patient awake for 1 or 2 minutes After a mild head injury a child, when left alone comfortably in bed, will often sleep so heavily that his state is mistaken for coma A head injury is an exhausting business, and fatigue is necessarily enhanced by, perhaps, several examinations at intervals It is admittedly difficult not to be anxious in such circumstances, and no neurosurgical unit would be critical of an appeal to transfer the child for observation

The Restless Case

A restless, struggling, noisy, violent, and inaccessible patient may be judged unconscious or stuporose—with justification, for he is almost certainly unaware of what he is doing and of what is going on around him But oligosyllabic labels such as " comatose and restless " are not adequate to describe this complicated and interesting state The patient can only be described as restless, struggling, noisy, violent, and inaccessible Such a state may be due simply to confusion and a distended bladder, and a determined effort at catheterisation may be rewarded with a quiet patient Otherwise restlessness may betoken headache with rising intracranial pressure from extradural bleeding, and suspicion may be increased if restlessness gives way within an hour or 2 to comparatively motionless coma For this reason sedatives should be avoided if possible, but if necessary intramuscular paraldehyde is the safest drug The state of consciousness then being no longer a yardstick, the development of lateralising signs must be depended on in the diagnosis of extradural hæmorrhage If the blood-pressure is raised at this stage contact should be made with a neurosurgical centre, for it seems that sometimes the blood-pressure may play leap-frog with rising intracranial tension

Lateralising Signs

When the state of consciousness has been assessed and recorded, one should look for the well-known inequality of the pupils, boggy swelling beneath the temporal muscle due to extravasated blood, hemiparesis, and a fracture in the temporal squama Any or all of these lateralising signs may be absent, but usually at least one of them indicates the side needing exploration

Very occasionally the pupil on the side of the hæmorrhage may for a time become smaller than its fellow before enlarging Typically the ipsilateral pupil becomes inactive to light and enlarges, and the contralateral pupil lags behind in undergoing the same changes When both pupils are fully dilated and fixed it is usually too late for treatment, and the patient's life may not be saved by evacuation of the clot When bleeding is brisk, the whole sequence of pupillary changes may take less than an hour, and the change from unilateral to bilateral dilatation happens only too often during the journey from the diagnosing hospital to a neurosurgical centre

An enlarged pupil does not always signify uncal herniation due to raised intracranial pressure A wound near the orbit may produce immediate traumatic midriasis, the third nerve itself may be torn, or the optic nerve may be damaged by distortion or contusion (confirmation of this being possible only when the patient becomes sufficiently conscious for blindness to be recognised)

Hemiparesis is almost always contralateral to the bloo clot If the patient is first seen in the late stages of dee coma hemiparesis may be impossible to recognise, and fo this reason all observers should record the reaction to pa of each limb early in the illness while the patient can sti respond

A decerebrate attitude may affect the limbs on one o both sides, or there may be decerebrate seizures, usuall in the form of tonic inversion of the limbs with or withou paroxysmal hyperpnœa or opisthotonus These ar danger signs and treatment must be immediate

Epilepsy after a head injury implies cerebral damag rather than compression by bleeding As a diagnostic ai it is not helpful, and if unilateral it cannot be depende upon to indicate the side of the extradural hæmorrhage

Surgical Treatment

The treatment of middle meningeal hæmorrhage should be in two stages—the immediate and the definitive

THE IMMEDIATE OPERATION

This must of necessity sometimes be the business of the general surgeon, for death may result from extradural hæmorrhage within 3 hours of injury to the head. It involves making a burr-hole in the skull to release blood clot under pressure, and suturing the scalp If the definitive operation of craniotomy is not to follow immediately, it is best to elevate the depressed dura by hitching it to the scalp with a special needle, as described later This is a simple operation, and it is extraordinary how even experienced surgeons will hesitate to do what is, after all, a great deal easier than an appendicectomy or tracheostomy

Conditions have changed remarkably in the past 25 years. In 1935 Symonds and Jefferson, discussing the treatment of extradural hæmorrhage by evacuation of clot and suppression of bleeding points through an enlarged burr-hole, warned the general practitioner that he might find himself obliged to operate to save life They wrote "Whether the General Practitioner will attempt the operation will naturally depend upon local and personal considerations which are outside the scope of this article If the progress of symptoms is rapid from hour to hour time is of the first importance, but when the development is measurable in terms of days there is usually opportunity for a carefully planned operation, and there is much to be gained from the services of a surgeon accustomed to the modern technique of cerebral surgery but in the case of dire emergency, and this may arise, the practitioner must operate and make the best of it." It may be added that the emergency, seemingly obedient to the quickened pace of living, nowadays rarely takes days to develop, and sometimes minutes count rather than hours Adams McConnell (1957), in a letter to *The Lancet* regarding extradural hæmorrhage, said "Many fruitless journeys into the country have convinced me that the local surgeon must assume responsibility for such cases."

Technique

General anæsthesia is neither necessary nor desirable. In very urgent cases time should not be wasted taking radiographs of the skull, and the appropriate side of the head should be shaved during preparation of the theatre trolleys The patient is placed on the table on his side, with a soft pad supporting the head If he is restless his wrists are fixed to the table by wide zinc-oxide strapping not restrained by a nurse Another broad band of strapping from side to side across the pelvis prevents him rolling off the table The proposed incision—2 in long—is marked out with a scratch or dye, infiltrated with 10 ml of local anæsthetic (adrenaline must not be added, for it increases blood-pressure and bleeding), and surrounded by drapes Most of the anæsthetic is injected into and beneath the scalp and little or none into the temporal muscle Suction apparatus is a necessity and diathermy very desirable

The incision—Three of the assistant's fingers must exert both firm pressure and separation on each side of the scratch to make the scalp tense, and a 2-in incision through scalp only is made between them If the pressure is properly applied there is no bleeding Each finger is then withdrawn in turn to release bleeding points for attention by the surgeon, who is armed with sucker in one hand and diathermy forceps in the other Using this technique it is best for a scrubbed nurse to wield the diathermy electrode Sometimes a retracted artery may necessitate the assistant withdrawing one hand to avert the scalp edge with toothed forceps

The main bogy which frightens surgeons unaccustomed to such work is that of bleeding—the brisk ooze coming from nowhere visible, of the artery spurting across the room, of messing about in a field of blood with an ill restless patient, and with fears of worse to come once inside But it is perfectly simple Admittedly, when incised, the scalp does not reveal its deep vessels readily as does subcutaneous tissue elsewhere, and therefore more trouble must be taken In plain words—a hasty slash made in the side of the head will get a surgeon into trouble—done methodically it is easy

When hæmostasis in the scalp has been achieved, a self-retaining retractor is inserted and the temporalis is incised down to the bone with either a knife or cutting diathermy Diathermy will not work if the muscle has been made œdematous with local anæsthetic Shreds of muscle adherent to the bone are scraped off and the bleeding points are again attended to, and only when the wound is dry is the retractor rearranged to include the muscle layer

The *perforator* is regrettably unfamiliar to most doctors not engaged in neurosurgery and yet the feel of its use is easily acquired at the expense of a few minutes practice in the postmortem room Its blade is sharpened to cut clockwise, and the shaft of the drill must be kept at right-angles to the skull surface The line of a fracture, if visible, is best avoided because it tends to make the perforator bind Pressure should be firm enough to transmit a sensation of cutting into the bone When the point has penetrated the whole thickness of the skull the sensation is coarser—that of grinding rather than cutting This is more easily appreciated if the speed of drilling is not too slow and timid, and it is a sign to lay aside the now dangerous perforator and use the burr, which will not harm the dura mater The Hudson burr, an effective and safe instrument, should be used boldly to enlarge the hole to useful dimensions, for provided $^1/_8$ in is still visible superficial to the bone, the burr cannot suddenly jump right through the skull, because of its conical form The diagnosis of extradural hæmorrhage is confirmed by the sight of black blood just visible through the tiny hole in the inner table made by the perforator (fig 1a) Once released by completion of the burr-hole, extradural blood-clot tends to force its way out into the wound, (fig 1b), perhaps with a trickle of fresh arterial blood also

If the case is comparatively late, the compressed brain may have lost its immediate power of recovery, it is locally collapsed, and the intracranial pressure is no longer sufficient to force out an appreciable quantity of clot Such a patient is in danger, and one should not hesitate to pass a large sucker through the burr-hole, manipulating it circumferentially as far as possible and aspirating all the clot presenting until the dura is exposed at the bottom of the cavity—perhaps an inch or more beneath the bone In such cases fresh bleeding will usually be scanty, and unless a bleeding point readily presents itself for coagulation it should be ignored for the moment

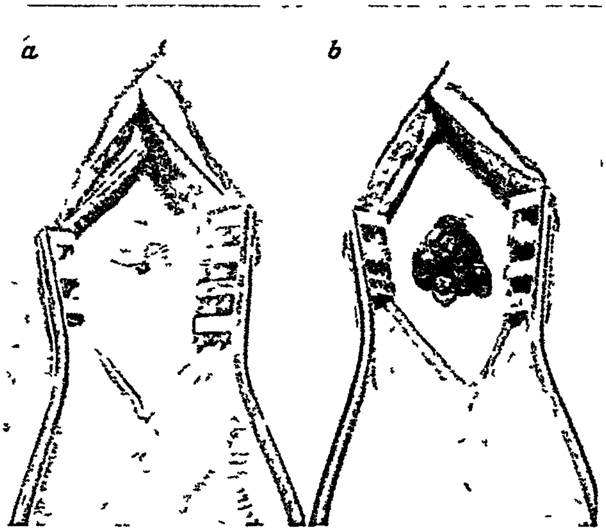

Fig 1—(*a*) Making a burr-hole enough has been done by the perforator, and black clot is just visible through a small hole in the inner table of the skull (*b*) Clot extruding after enlargement of the hole to about 1 cm with a burr proves the diagnosis of extradural hæmorrhage

In the fulminating case, with rapid deterioration of consciousness since injury (within, say, 30 minutes to 4 hours) and early operation when intracranial pressure is at its height, the brain will be under sufficient tension to force a more copious and useful quantity of clot to the surface

In either of the above instances the general surgeon has two courses open to him

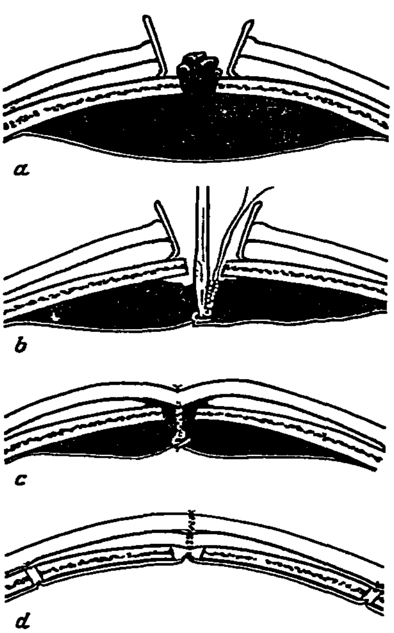

Fig 2—Sectional diagrams depicting (*a*) spontaneous extrusion of extradural clot after use of the burr, (*b*) the dura mater, which is lax and wrinkled, transfixed by the dura-elevating needle (*c*) the emergency operation completed, and (*d*) the normal relations after craniotomy

1 After sucking away presenting clot, he may do nothing further except to suture the scalp closely When this is completed a dilated pupil may already have diminished in size During the journey to a neurosurgical centre bleeding and extrusion of clot tend to make a tense swelling beneath the scalp Blood may ooze through the wound a little, but the patient will not bleed to death The reason for insistence on absolute hæmostasis in scalp and temporal muscle is now apparent, for bleeding from these sources would lose all the advantage gained by decom-

pression For the same reason, on no account must a firm crepe bandage be applied to the head, for pressure on the scalp is pressure on the brain, and it entirely defeats the object of decompression The surgeon should personally supervise the application of a loose cotton bandage In my experience this method allows about 30 minutes' grace in a rapidly progressing case with fresh bleeding, and after this the pupil again dilates

2 The safer course is to hitch up the dura to the scalp by means of a specially designed hooked needle The dura is transfixed with the (previously threaded) needle mounted on a needle-holder, either before or after bold aspiration of all clot within reach It is not even necessary to see the dura, a fold of which is caught up quite easily after the first or second " scrape along the bottom " (fig 2b) As soon as good purchase is obtained, one end of the thread is passed through a large bite of scalp at the top of the wound After a few moments of rather firm steady traction, the suture is tied The surgeon should not be disappointed if the dura does not rise completely to the skull, for there is considerable suction beneath it, and the brain takes time to expand The needle is shaped to avoid damage to any underlying cerebral blood-vessel Again temporalis is left gaping, fresh bleeding is ignored, and the scalp is sutured in one layer (fig 2c) This method should give considerably longer than 30 minutes' grace for travelling time Though clot beneath the temporal lobe and round the periphery remains to be dealt with at the definitive stage, dural anchorage roughly at the centre of the depression relieves the brain to some extent, and especially prevents further depression due to fresh or continued bleeding

Either of the above immediate operations should take only 20 minutes, even if it is the surgeon's first adventure in this field

Siting of the Burr-hole

An extradural hæmorrhage from a torn middle meningeal artery (much the commonest cause) which is endangering life is of at least 3 in diameter, hence a burr-hole anywhere within this circumference will find it (fig 3) One need not depend on measurements to expose the middle meningeal artery itself, no useful purpose is served by exposing the artery in the temple because the bleeding is very often far down on the floor of the middle cranial fossa Unless radiographically a fracture has been demonstrated crossing the groove of the posterior branch of the middle meningeal artery, a burr-hole should be made in the anterior position (A in fig 3), roughly mid-way between eye and ear If the search here meets with no success or with a thin film of clot only, a second hole should be made 3 in behind and slightly above it (B in fig 3)

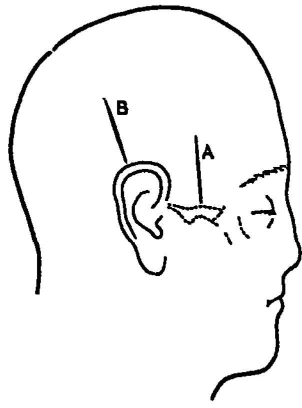

Fig 3—In the great majority of cases of middle meningeal hæmorrhage, exposure at either A or B will find it The incisions need not be oblique, but this conveniently corresponds with the temporal muscle-fibres

When hemiparesis is the only lateralising sign, negative findings at both A and B may be taken as evidence of cerebral contusion or laceration The dura should not be incised unless it is obviously blue (I have attributed hemiparesis to an ipsilateral extradural hæmorrhage once only, had not the weakness recovered immediately the clot was evacuated, I should have had to invoke a contralateral cerebral contusion) If the patient is already at a neurosurgical centre fruitless explorations at the rarer sites (e g , under the frontal lobe) may be cut short by angiography But such explorations are necessary only when temporal swelling is absent and the scalp injury or

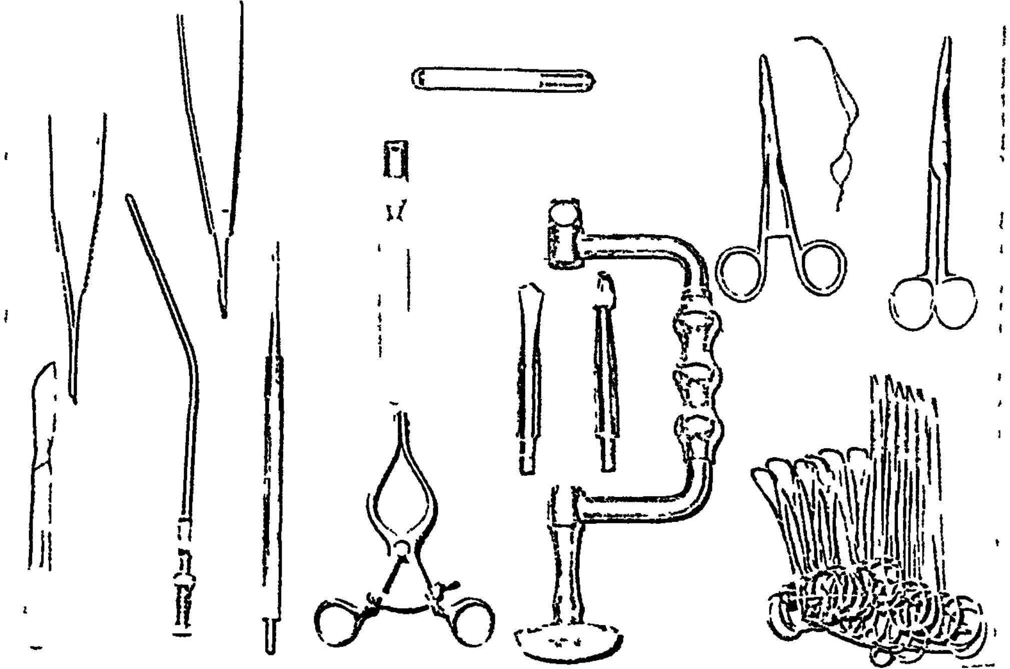

Fig 4—The basic instruments for the emergency operation for extradural hæmorrhage

From left to right knife, toothed forceps, large sucker, diathermy forceps, diathermy electrode, self-retaining retractor, periosteal elevator, towel clips, tube of strong braided silk, Hudson brace with no 4 perforator bit and matching burr, needle-holder and dura-elevating needle, scissors, and artery forceps (The dura-elevating needle is made flat from tantalum sheet, it can be used only for this purpose, and no other needle will serve) fracture is remote from the temple—and these cases are best dealt with from the first by a neurosurgeon

THE DEFINITIVE OPERATION

This neurosurgical procedure is performed through a standard osteoplastic flap only after the emergency operation has been completed.

The turning of a flap has previously been recommended for extradural hæmorrhage. Hooper (1959) said it was sometimes necessary, and Loyal Davis (1946) favoured it, but Oliver (1958) was the first to rationalise craniotomy by previously determining the extent of the clot. Craniotomy has probably not become standard neurosurgical practice for two reasons (1) because surgeons thought at the moment it would be quicker to nibble away " to the size of a florin ", and to secure the bleeding-point with the aid of suction, diathermy, ligatures, or match-sticks, and (2) because, though the flap might be superior, turning it would be calamitous if an extradural clot were either not found or found in an unexpected position.

For the past 5 years I have used the temporal burr-hole to confirm the diagnosis, to relieve excessive pressure, and to measure—by feeling with a Gigli-saw guide—the extent to which the dura has been stripped. For the last purpose Oliver (1958) uses a malleable probe, and this is possibly better than a guide, which I have sometimes found to give a false measurement on striking a bony irregularity

In this respect the emergency operation differs when done by a neurosurgeon. If this stage-I operation has already been performed elsewhere, the burr-hole is reopened. A seeker introduced through the clot as far as it will go is withdrawn and placed in a corresponding position over the scalp A dye mark is made $^1/_2$ in. beyond its tip In this way probings repeated in anterior, posterior, and upward directions determine the scalp incision. The ring of burr-holes, sited $^1/_2$ in. within the incision, then corresponds with the limits of the clot in all directions except downwards, where clot may be assumed to extend beneath the temporal lobe The wide bone removal facilitates the search for bleeding over the floor of the middle fossa, it makes possible complete removal of all clot, and control of the many small bleeding-points which result from separation of bone from dura—and which need attention just as much as in dural separation at any craniotomy During reposition of the bone-flap the dura in the centre of the field is hitched up to the temporalis by a stitch passing through the stage-I burr-hole, which has been left open during craniotomy.

Liaison

Neurosurgical centres welcome telephone consultations with any hospital holding a case of head injury which is deteriorating The likelihood of extradural hæmorrhage, correlation between its possible position and the site of any visible injury to the scalp, degree of urgency, and other injuries the patient may have sustained, all must be discussed, and the plans for a given case should be put into action before even one pupil is fully dilated. In extradural hæmorrhage the degree of urgency correlates with the rate of bleeding, the more profuse the hæmorrhage the more rapid the patient's downward course and the more likely he will need immediate treatment on the spot. For instance, a patient conscious on arrival with pupils of 4 mm. who becomes restless or drowsy and whose pupil enlarges to 7 mm within an hour, should not be moved to a neurosurgical centre 2 hours' journey away, he should have his emergency burr-hole completed within 30 minutes of the telephone consultation, and meanwhile an ambulance should be organised to stand by As soon as the diagnosis is confirmed by burr-hole, a message is sent asking the police to escort the ambulance (the police are most obliging, enter into the spirit of the emergency, and, if the truth be told, rather enjoy it!) Unconscious cases are transported prone, for a tracheostomy and aspiration of vomit on arrival diminishes the patient's chances of survival.

Conclusions

Responsibility for the treatment of middle meningeal hæmorrhage has, with the development of fast transport and neurosurgical services, shifted too universally to remote specialised units To reduce mortality, in selected cases, the treatment should be shared, and the more urgent the case, the more desirable are a general surgeon's services

All hospitals accepting major accidents should carry certain instruments (fig 4) enabling a lifesaving burr-hole to be made, and both consultant surgeons and resident surgical officers should be familiar with their use They are best kept in a special drum, autoclaved at intervals

I have found that the technique of saving life by emergency operation is aided by a special needle enabling the dura mater to be elevated through a burr-hole After personal tests I think it is worthy of trial by general surgeons, for its value can only be proved on a large number of cases in which two-stage treatment is necessary

The orthodox creeping craniectomy for extradural hæmorrhage is clumsy, inaccurate, and often slow. I would even, with some trepidation and due homage to its honourable history, condemn it as no longer worthy of inclusion among neurosurgical techniques

Instruments mentioned in this article may be obtained from Messrs. Lewis Bros , Marylebone High Street, London, W 1

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THE SMALL BLOOD-VESSELS OF THE CONJUNCTIVA AND NAILBED IN DIABETES MELLITUS

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WITH the renewed interest in the microcirculation, Ditzel et al (1958) have examined the small blood-vessels of the conjunctiva in diabetes mellitus and have reported significant findings In the present work, following on the examination of the small vessels of the conjunctiva and nailbed in health and certain diseases (Davis and Landau 1960), our findings in diabetes are reported.

Methods

The group consisted of 75 diabetic patients, of whom 22 were between forty and fifty-six years old and the remainder above that age The blood-pressure was raised in 25 and normal in 50 Of the latter, 28 showed signs of arteriosclerosis of heart, cerebral vessels, or peripheral vessels Diabetic retinopathy was present in 20 patients and included all grades of severity The duration of the diabetes was less than one year in 2 patients, one or two years in 22, three to five years in 17, six to ten years in 28, and fifteen to twenty-two years in 6

The conjunctival and nailbed vessels were examined by slit-lamp and microscope, by the techniques already reported (Landau and Davis 1957), and often photographed The diameter of representative vessels was measured In all patients the small blood-vessels were investigated for

1 Venous congestion in the conjunctiva, and congestion of the venous limb of the nailbed capillary In over 70% of healthy persons the smaller venules of the conjunctiva do not exceed 25 μ in diameter When the diameter of these vessels exceeded 33 μ they were called congested (fig 1) The venous limb of the nailbed capillaries in health does not exceed 12 μ in diameter A diameter greater than 12 μ was called congested (fig 3)

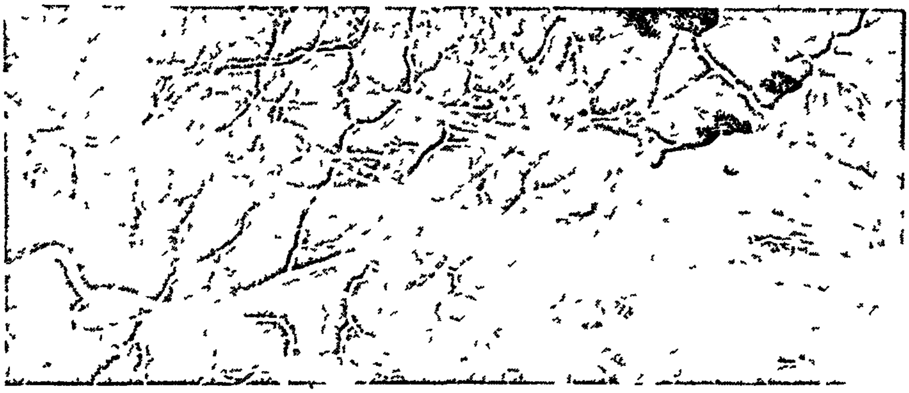


Fig 1—Venous congestion in conjunctiva of diabetic (× 11 5)

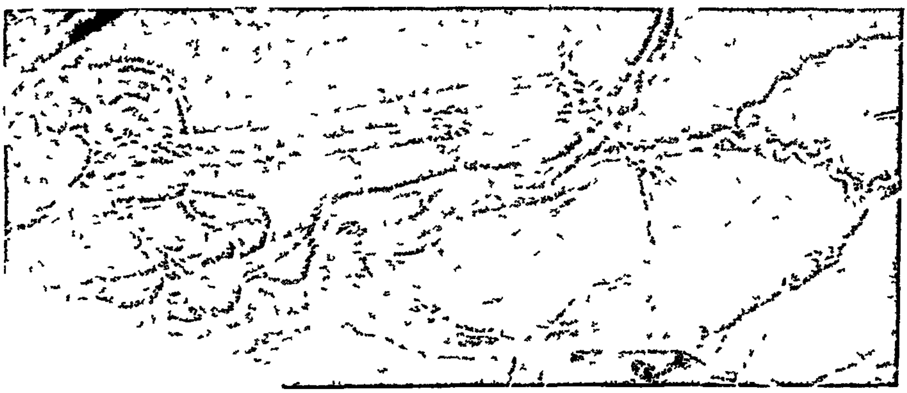


Fig 2—Arteriosclerotic pattern in conjunctiva of diabetic (× 11 5)

2 Severe capillary narrowing A capillary diameter of 3 5 μ or less was termed severe narrowing In the nailbed the measurement is of the arterial limb of the capillary

3 The presence of an arteriosclerotic pattern (Davis and Landau 1960) in conjunctiva and nailbed (figs 2 and 4)

4 The height of the terminal digital vessel blood-pressure (Davis 1953, Davis et al 1959)

5 Micropools (we prefer this non-committal term to microaneurysms) of all types in the conjunctiva were sought, examined, and photographed (Cook 1954)

Exactly the same blood-vessel investigations were done on 65 healthy persons, 140 patients with hypertension, and 110 patients with clinical complications of arteriosclerosis

Results

The results are given in the table The following features were found in diabetes mellitus

1 Venous congestion was very common both in the conjunctiva and in the venous limb of the nailbed capillary

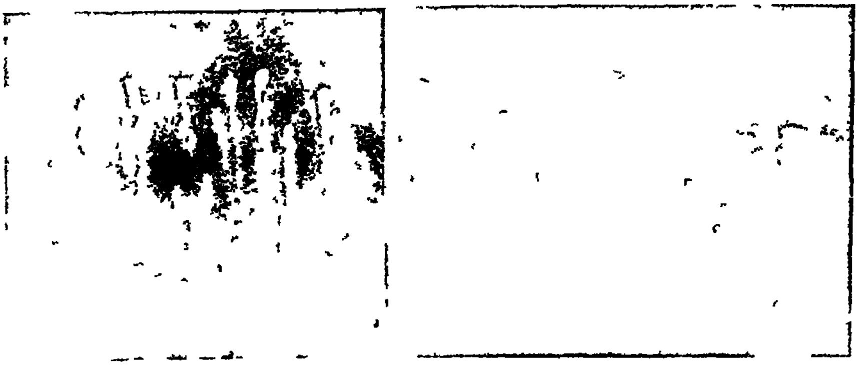
2 Severe capillary narrowing in the conjunctiva was commoner than in any group other than hypertension, and was seen particularly in diabetics with severe complications

3 An arteriosclerotic pattern in the conjunctiva was commoner than in any group other than arteriosclerosis The pattern was also common in the younger diabetics investigated, occurring in 8 of the 22 patients aged forty-six to fifty-six and in 4 of the 8 patients aged forty to fifty The pattern consists essentially of straight, long, thin unkinked arterioles, accompanied by parallel or sinuous dilated venules

4 Blood-pressure in the terminal digital vessel was found t be high in 10 of the 50 diabetic without hypertension and in 1 of the 25 diabetics with hypertension The hypertensive diabetics with high terminal-digital vessel pressure were prone t severe complications

5 Micropools were not infrequent, but not commoner than in hypertension

A characteristic blood-vessel picture emerged for diabetes mellitus in general, but not a diagnostic picture



(a) (b)

Fig 3—Congestion of venous limb of capillary in nailbed of diabetic (a, × 40, b, × 90)

Fig 4—Arteriosclerotic pattern in nailbed of diabetic (× 40)

CAPILLARY FEATURES AT AGE 40 OR ABOVE (INCIDENCE %)

—	Healthy persons no (65)	Hyper-tension (140)	Arterio-sclerosis (110)	Diabetes mellitus (75)
Venous congestion				
Conjunctiva	28	22	32	60
Nailbed, venous limb of capillary	8	14	7	49
Severe capillary narrowing				
Conjunctiva	6	53	10	43
Nailbed	4	33	13	15
Arteriosclerotic pattern				
Conjunctiva	10	28	71	45
Nailbed	12	24	43	24
High terminal-digital-vessel pressure	3	48	11	31
Micropools	5	24	19	25

for individual patients When the 75 diabetic patients were divided into two groups, above and below fifty-six years old, no conspicuous differences emerged The incidence of venous congestion was not influenced by age In the age-group forty to fifty, the arteriosclerotic pattern was commoner in diabetics than in any other condition investigated (except arteriosclerosis with clinical complications) As regards the frequency of the various findings, only severe capillary narrowing in the conjunctiva appeared to be related to the duration of the diabetes The 6 severest examples of diabetic retinopathy were found in diabetes of duration of four, five, eight, ten, eighteen, and twenty-two years, while the severest capillary narrowing in conjunctiva or nailbed—usually associated with increased pressure in terminal digital vessels—was seen in 13 patients with a duration of four to ten years (mean seven years), in 1 with a duration of two years, and in 4 with a duration of half or one year Severe capillary changes, as distinct from the frequency of the various changes, were commonest in diabetes of long duration

Discussion

As the diabetic patients were all over forty, the findings reported are those of middle age and the old Venous congestion was the most prominent and common finding In this we confirm Ditzel (1956) and support Ballantyne (1945) who demonstrated venous congestion in the retina in diabetes Our finding of frequent and well-marked congestion of the venous limb of the nailbed capillary strikingly confirmed one of the basic lesions of diabetes, emphasised hitherto only in the retina and conjunctiva

The high incidence in diabetics—particularly the younger ones—of the special pattern of the small vessels which we have shown to be characteristic of arteriosclerosis is further evidence of the close connection between diabetes and arteriosclerosis, and the tendency of the younger diabetic to arteriosclerosis In some diabetics the pattern was the first evidence of arteriosclerosis

The severe capillary narrowing seen in the conjunctiva in diabetes is similar to that described by us in hypertension and conformed to the conjunctival vascular pattern-change II of Ditzel (see below) The incidence of this narrowing in the 50 diabetics with normal blood-pressure was much the same as in the 75 diabetics in the whole series, including the 25 hypertensive patients Venous stasis could result in increased terminal arteriolar and capillary blood-pressures

As for micropools in the conjunctiva (Ashton 1949, 1959, Friedenwald 1950, Cook 1954, Ditzel 1959), they were equally common in hypertension and diabetes, somewhat less common in arteriosclerosis, and rather rare in the healthy We have also found micropools from time to time in patients with everyday chronic medical diseases, such as chronic bronchitis and chronic arthritis, in the absence of diabetes, hypertension, or clinical arteriosclerosis Of the diseases studied, only in hypertension did the incidence of micropools reach that of diabetes

In diabetes Ditzel (1956) laid stress on the occurrence in the conjunctiva of venous congestion, capillary elongation, and intravascular red-cell aggregation The present work confirms (and extends) the finding of the venous congestion, but, while we have often seen capillary elongation and red-cell aggregation, our non-diabetic patients above the age of forty have shown them quite often It is possible that capillary elongation is more specific for the young diabetic (Ditzel and Duckers 1957)

Ditzel et al. (1958) have described two abnormal vascular conjunctival patterns in diabetes Vascular pattern change I was characterised by a general vascular distension. The ratio of the arterial/venous diameter, normally 1/3 to 1/2, became 1/4 to 1/8 Change II was marked by a general constriction of all vascular elements Most true capillaries were completely invisible and the tissue ischæmic Many arterioles were closed All his diabetics with conjunctival vascular pattern-change II had severe vascular disease (retinopathy and nephropathy), while those with change I had less evidence of vascular disease, but more than in those diabetics with normal conjunctivæ Our 75 patients included 11 with severe diabetic and vascular complications Of these 11, 8 had pattern-change II and 3 change I We agree that pattern II is common in severe diabetes, but we have shown it to be a feature of severe hypertension (Landau and Davis 1957, fig 3, Davis and Landau 1958) and have also seen the pattern in other conditions

Diabetes was associated with characteristic but not pathognomonic changes in the small vessels of conjunctiva and nailbed—namely, venous congestion and congestion of the venous end of the capillaries, an arteriosclerotic pattern in the conjunctiva (particularly in the age-group forty to fifty), severe capillary narrowing in the conjunctiva, and an increased incidence of high pressure in the terminal digital vessels

Summary

The small blood-vessels of the conjunctiva and nailbed were examined in 75 diabetics and compared with those of 140 hypertensive and 110 arteriosclerotic patients, and 65 healthy persons—all aged forty or more

Venous congestion in the conjunctiva was found in 60% of the diabetics The venous limb of the nailbed capillary was also commonly congested The basic diabetic lesion of capillary congestion on the venous side has thus been found elsewhere than the eye

An arteriosclerotic pattern of the small vessels of the conjunctiva was common in diabetics, and particularly frequent in comparison with the other conditions at ages from forty to fifty

Severe capillary narrowing in the conjunctiva was common, and a high pressure in the terminal digital vessels not uncommon, in diabetics

The incidence of conjunctival micropools in diabetes was appreciable (25%), but although much commoner than in the healthy they were only slightly commoner than in arteriosclerosis and no commoner than in hypertension

Diabetes was associated with characteristic but not pathognomonic changes in the small blood-vessels of the conjunctiva and nailbed

Thanks are due to Mr M Ivry for photographs and skilled observations

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PSEUDOMONAS PYOCYANEA WOUND INFECTION

AN OUTBREAK IN AN ORTHOPÆDIC UNIT

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IN well-run orthopædic units wound infection is unusual and outbreaks due to *Pseudomonas pyocyanea* must be rare In burns units and urological units this organism is a well-known hazard

The outbreak, described here, among patients under treatment for fractures, was unexpected and disquieting

Outbreak and Investigation

On April 28, 1959, a patient (case 1, table I) was admitted to the male ward of the unit He was unconscious and had severe injuries of the head, chest, and lower limbs Treatment with 1,000,000 units of penicillin four-hourly was started, and next day an emergency tracheostomy was carried out in the "plaster room" In spite of regular bronchoscopy, a tracheobronchitis developed and *Ps pyocyanea*, *Staphylococcus aureus*, and β-hæmolytic streptococci were cultured from a swab of the bronchial secretions taken on April 30 The strain of *Ps pyocyanea* was sensitive to streptomycin and chloramphenicol

Six days later 3 other patients (cases 2–4) were found to have *Ps pyocyanea* wound infections and it seemed likely that case 1 was disseminating the organisms as an aerosol from the tracheostomy tube Cases 1, 2, and 4 were accordingly transferred to a side-ward for barrier nursing

Case 3, however, was a patient in the female ward.

In the male ward, examination of dust, curtains, and blankets, as well as air sampling with the Bourdillon slit sampler in the neighbourhood of case 1, revealed a low level of air contamination (100 colonies per c ft) and no *Ps pyocyanea* These negative findings, and the infection of a patient in the female ward, attracted attention to the plaster-room, where case 1 had had his tracheostomy and where all 4 patients had received treatment It was now discovered that the plaster-encrusted bucket (fig 1) used for soaking plaster-of-paris bandages contained *Ps pyocyanea* among other organisms As *Ps pyocyanea* was not found elsewhere in the plaster-room (table II), the bucket was thought to be the source, and it was replaced

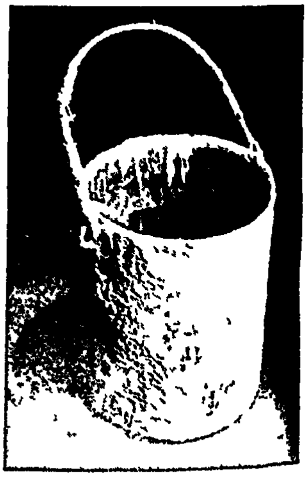

Fig 1—The plaster bucket.

Infection, however, continued (cases 5, 6, 7, and 8), and further search was made for a possible primary source, assuming now that the bucket had been secondarily contaminated

Cultures of plaster-of-paris in the form of powder and ready-made bandages grew no *Ps pyocyanea*, but this organism was found in large numbers in cultures from the cellulose wadding ("wood wool") used as padding under all plaster casts applied for fresh fractures All the infections were in patients to whom padded plasters had been applied for the treatment of fractures which were either compound or were accompanied by skin abrasions in the region included in the plaster In all the compound

TABLE I—CASES IN ORDER OF THEIR DISCOVERY

Patient	Fractures	Operation	Initial treatment	Pyocyanea isolated	Result
1	Tibiæ and fibulæ (one compound)	April 25 (tracheostomy)	Debridement. Long leg plaster	April 30	Died from head injury
2	Compound Pott's	April 23	Debridement, internal fixation Short leg plaster	May 6	Healed, second intenti
3	Compound tibiæ and fibulæ	April 2	Debridement, open reduction Steinmann pins in long leg plaster	May 6	Pin track infection early Healed
4	Bilateral os calcis (one compound) Tibia, closed	April 22	Debridement, manipulation Long leg plaster	May 6	Split skin graft to heel
5	Compound tibia and fibula	May 3	Debridement, closed reduction Long leg plaster	May 14	Healed, second intentio
6	Right tibia and left Pott's Abrasion	May 7	Manipulation and long leg plaster Open reduction and short leg plaster	June 22	Split skin graft, right th
7	Compound tibia and fibula with degloved skin	May 30	Internal fixation Skin defatted and put back	June 15	Infection at fracture s Late pedicle graft
8	Pott's Abrasions	June 27	Manipulation and plaster *	July 22	Split skin graft, ankle

* Initially treated as outpatient in casualty department.

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TABLE II—ORGANISMS ISOLATED IN PLASTER-ROOM

Source	Organisms	Degree of contamination
r	*Bacillus spp*, *Staph albus*, *Sarcina spp*, coliforms, moulds	40 colonies per c ft.
ust	*Bacillus spp*, *Cl welchii*	Moderate
on-sterile instruments*	No growth	
able top	No growth	
loor	*Bacillus spp*, *Cl welchii*, coliforms	Severe
ubber mats	Coliforms, *Staph albus*, *Staph aureus*	Severe
ater-supply	*Bacillus spp* †	Slight (c. 40 colonies per ml.)
ir-filters	No growth ‡	

* e.g, plaster shears
† Probably derived from the tap
‡ The filters were impregnated with soot. Tests showed this to be toxic for a laboratory strain of *Staph albus*

ractures skin closure had been achieved after wound xcision, and the suture line had been covered with everal layers of sterile gauze and a layer of sterile cotton-vool before cellulose wadding and plaster-of-paris were pplied Some, but not all, operations had been done after he application of a pneumatic tourniquet, the limb having een exsanguinated by an Esmarch bandage The abraions accompanying simple fractures had been cleaned vith cetrimide and chlorhexidine before being covered vith sterile gauze, cellulose wadding, and plaster

The Esmarch bandage kept in the plaster-room was ound to be heavily contaminated with *Clostridium welchii*, *Staph aureus*, *Staph albus*, coliforms, and aerobic spore-forming bacilli, but *Ps pyocyanea* was not isolated

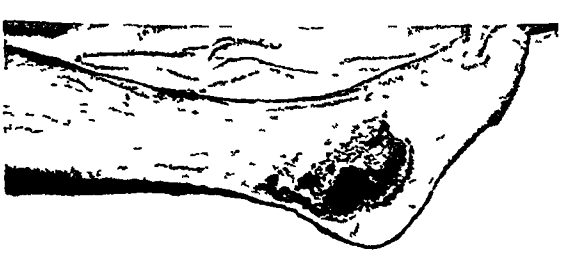

Fig 2—Extent of ecthyma gangrenosum in patient 8

Effect of Infection

The effect of *Ps pyocyanea* infection is best illustrated by examples

PATIENT 6 had simple fractures of the left ankle and right upper tibia The left Pott's fracture was treated by operative screw fixation of the medial malleolus and did not become infected The right tibial fracture was associated with multiple abrasions on the shin and did not have the covering of sterile wool that was used for the left ankle Because of associated instability of the knee, the long leg plaster on the right leg was untouched for six weeks On its removal a moderate amount of green pus was encountered and an area of full-thickness skin loss, 3×6 in, was found in the region of the skin abrasions Culture of the pus produced a pure growth of *Ps pyocyanea* The raw area cleaned up rapidly with daily dressings of 'Polybactrin' (polymyxin-bacitracin-neomycin) spray and soft-paraffin gauze, and was ready for successful split-skin grafting after two weeks

PATIENT 7 had sustained a severe compound fracture of the right tibia and fibula with an extensive "degloving" injury of the overlying skin Screws were used to fix the fracture and total cover was obtained using the skin available, though part of this was "defatted" and used as a full-thickness free graft Sterile gauze and wool were covered with cellulose wadding before plaster-of-paris was applied. An area 2×3 in of the "graft" sloughed, and the associated *Ps pyocyanea* infection called for removal of the bone screws Subsequent treatment included sequestrectomy and required the transfer of a tubed skin pedicle from the abdomen This was timed to give full-thickness skin cover of the incompletely healed fracture site by the time the infection had been controlled.

In the most troublesome cases, the infection led to full-thickness skin loss The appearances (fig 2), which have been described (Wilson and Miles 1955) as "ecthyma gangrenosum", were uniform in that the area of skin loss became well demarcated and the dead black slough separated relatively early to leave a base that was rapidly made clean enough for grafting In spite of this ease of handling of the complication, treatment was lengthened in nearly all the patients

Non-pathogens

Non-pathogenic aerobic spore-forming bacilli were isolated from the cellulose wadding and from apparently infected wounds of the patients listed in table III, none of whom had *Ps pyocyanea* infections These patients showed no ill effects and they are reported only as further evidence that the *Ps pyocyanea* infections originated in the cellulose wadding

Sterilisation of Cellulose Wadding

As soon as it was shown that the cellulose wadding was contaminated with *Ps pyocyanea*, sterilisation was undertaken

Rolls of wadding 3 in and 6 in wide are supplied to the hospital in packages of 12 The rolls are $2^{1}/_{4}$ in and $2^{3}/_{4}$ in. in diameter, they are relatively tightly wound and have a covering of tissue paper which is open at both ends

Tests with Browne's steriliser control tubes indicated that a sterilising temperature was attained in the centre of rolls Additional tests with thermocouples in an experimental autoclave showed that the time-lag between the temperature in the inside of the dressings drum and the temperature in the centre of a roll was insignificant Autoclaved wadding proved to be sterile

All the wadding has since been autoclaved at 15 lb (121°C) for twenty minutes before use and no further incidents of infection have come to light The material deteriorates a little through sterilisation but not enough to interfere with its use

TABLE III—CASES WITH AEROBIC SPORE-FORMING BACILLI *

Patient	Admission	Fracture	Operation	Treatment	Positive swab
9	June 2	Closed tibia and fibula blisters	June 2	Manipulation and plaster †	June 2
10	June 2	Compound tibia and fibula	June 2	Debridement, open reduction and suture	June 24
11	Aug 16	Closed tibial table	Aug 16	Open reduction internal fixation and plaster	Aug 20

* The aerobic spore-forming bacilli isolated were unlike those isolated from the water-supply but similar to those isolated from the wadding
† Initial treatment on May 30 given elsewhere Admitted with plaster blisters

Discussion

In these cases *Ps pyocyanea* almost certainly reached the wounds, or their sterile dressings, in water which had been expressed from a wet plaster bandage and contaminated by passage through the infected cellulose wadding Oozing or bleeding can help to form a " nutrient bridge " by which organisms may migrate If plaster bandages are soaked in contaminated reservoirs (e g , the bucket), the hazard is even greater

Though the Esmarch bandage was a potential source, no actual infections from its use were discovered This may have been because the skin was carefully cleaned before any operative procedure and wounds associated with compound fractures were always excised Nevertheless, it seems desirable to treat Esmarch bandages regularly with an effective antiseptic

The most important lesson of this outbreak is the importance of proper sterilisation of all dressings—even those remote from actual wounds

Summary

An outbreak of *Pseudomonas pyocyanea* infection in an orthopædic unit was traced to contaminated cellulose wadding (wood wool) The importance of routine sterilisation of all dressings—even those remote from wounds—is emphasised

We wish to thank Prof J W Howie and Prof R Barnes for their interest and help in this investigation

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CHROMOSOME COUNT IN A HERMAPHRODITE WITH SOME FEATURES OF KLINEFELTER'S SYNDROME

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IN 1956 Tjio and Levan, analysing the chromosome complement of normal lung fibroblasts derived from a series of aborted human fœtuses, demonstrated that these cells each had 46 chromosomes Shortly afterwards Ford and Hamerton (1956), working with testicular tissue, confirmed this figure It is now accepted that man has a diploid chromosome number of 46–22 pairs of autosomes and a single pair of sex chromosomes, XX in the female and XY in the male The revolutionary techniques used by these workers were soon applied to the study of human congenital malformations, and at least twenty different chromosomal anomalies have been shown to be associated with clinical abnormalities Undoubtedly other similar associations remain to be discovered

Among the first human disorders to be analysed for chromosome number and morphology was Klinefelter's syndrome (Jacobs and Strong 1959, Ford et al 1959a and b, Stewart 1959, Crooke and Hayward 1960, Bergman et al 1960) The chromatin-positive cases of Klinefelter's syndrome so far described have 47 chromosomes—presumably 22 pairs of homologous autosomes and an XXY sex-chromosome-complement

We report here a case which presented some of the clinical features of Klinefelter's syndrome—a diagnosis which was strengthened by the finding of chromatin-positive nuclei in the buccal smear Chromosome analysis, however, did not confirm this diagnosis and stimulated a search for ovarian tissue The patient, is, in fact, a lateral hermaphrodite with an ovary and a testis

Cases of hermaphroditism are exceedingly rarely reported, and until 1959 only about 88 had been recorded (Lewis 1959) Of these, 8 have had their " chromatin state " recorded Only in 2 cases have the chromosome number and morphology been reported (Harnden and Armstrong 1959, Hungerford et al 1959) We report a 3rd case

Case-record

In 1956, at the age of 11 years, the patient presented because of pronounced penile hypospadias, the opening of the urethra being some 4 5 cm from the tip of the glans At that time there were no secondary sex characteristics, the left testis could not be palpated, and the right testis was in the scrotum and felt normal In other respects he seemed a normal boy The hypospadias was repaired by the Denis Browne operation, and the functional result was sufficiently satisfactory to justify discharge from the follow-up clinic a year later

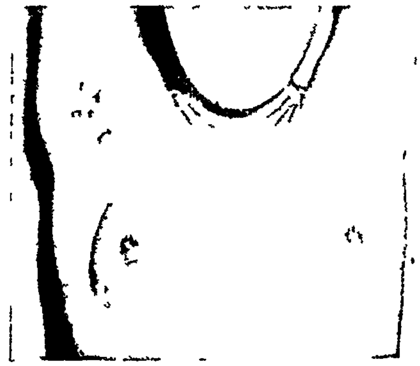

Fig 1—Gynæcomastia with distinct development of nipple and areola, and axillary hair

In 1960, aged 14 years, he was referred again because, as he had advanced in puberty, it was noticed that his breasts were enlarging much more than was thought to be normal for a boy of his build (fig 1) He was finding this a very great embarrassment at school and was anxious to have something done about it He was quite tall (5 ft $4^{1}/_{2}$ in) and thin (body-weight 7 st 10 lb) and of eunuchoid proportions (span 5 ft 7 in., U/L 0 87, head to pubis 30 in , pubis to feet $34^{1}/_{2}$ in (fig 2) His intelligence appeared to be of low average, and he was of a quiet but pleasant disposition His voice was partially broken, but he had no facial hair He did, however, have plenty of pubic and axillary hair, but the former was of feminine distribution (fig 2) The right testis was in the scrotum and was of normal consistency, but felt slightly smaller than would be expected for his degree of maturity (fig 3) The left testis could not be palpated in the scrotum, nor in the inguinal canal. He had pronounced gynæcomastia with well-developed nipples each surrounded by a distinct areola On clinical examination the other systems were entirely normal

Initial investigations revealed that he had a normal output of 17-ketosteroids and ketogenic steroids (3 9 and 7 4 mg per day respectively) His white-blood-cell count was 8300 per c mm. with a normal differential count Female " drumsticks " were

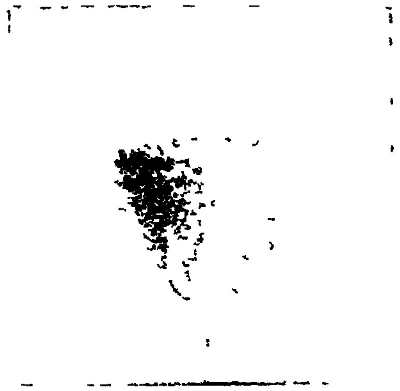

Fig 3—Pubic hair and genitalia the penis is of reasonable size but only right testis can be seen in scrotum

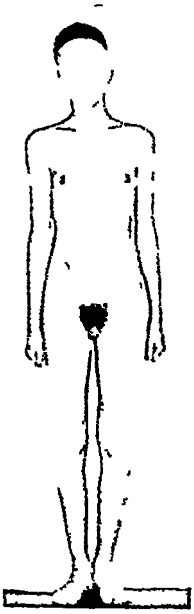

Fig 2—Configuration of the patient, showing feminine distribution of pubic hair

present in the neutrophils, and the buccal smear confirmed that he was " chromatin-positive " It was at this stage that we felt he represented chromatin-positive Klinefelter's syndrome, and accordingly it was decided that bilateral mastectomy should be undertaken. This was done, and at the same time testicular biopsy and marrow puncture were performed.

Testicular biopsy (fig 4) showed that varying degrees of tubular atrophy had occurred as a result of intratubular fibrosis and collagen deposition some tubules had atrophied completely Surviving tubules were lined solely by Sertoli cells, and no evidence of spermatogenesis was present. The interstitial cells, which were somewhat reduced in quantity, were in small clumps lying in a loose stroma The appearances were similar to those described by Ferguson-Smith (1959) and Plunkett and Barr (1956) in some cases of chromatin-positive Klinefelter's syndrome

Chromosome analysis—Bone marrow specimens, obtained by sternal puncture, were treated by a modification of the method described by Ford et al (1958) Squash preparations were made from the final, Feulgen- and aceto-orcein- stained, cell suspension These were searched systematically for cells in metaphase of mitosis Forty-two cells, in which the chromosomes could be counted accurately, were recorded. Thirty-nine cells each contained 46 chromosomes, and in no cell were 47 chromosomes counted. The results were as follows

No of chromosomes				
<45	45	46	47	>47
2	1	39	0	0

Sex chromosomes XX. No chromosomal abnormality apparent.

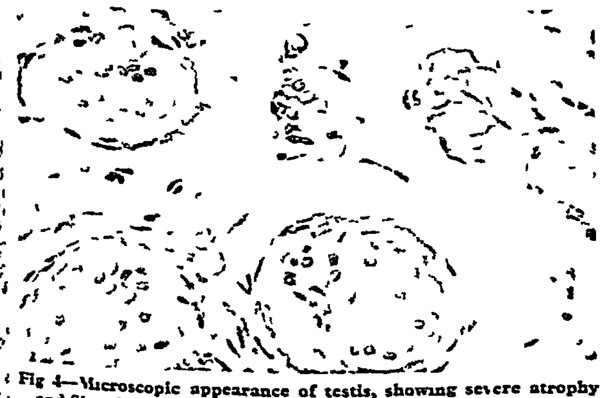

Fig 4—Microscopic appearance of testis, showing severe atrophy and fibrosis of tubules and complete absence of spermatogenesis.

Chromosome morphology was examined in six cells Each cell appeared to contain a set of 23 pairs of chromosomes as in a normal female.

Hormone assays showed that the excretion of urinary gonadotrophins was 24 mouse units per day (normal 8–48 mouse units) There was a normal output of 17-ketosteroids (as has already been mentioned), but the urinary excretion of œstrogens (60 I U per day) was in excess for a boy of this age (normal 8–26 I U per day)

Diagnosis—The normal output of gonadotrophins, the high output of œstrogens, and the absence of the left testis were somewhat against the diagnosis of Klinefelter's syndrome. Above all, however, the chromosome analysis, although confirming the presence of two X chromosomes, excluded the diagnosis since the Y chromosome was absent. The most likely alternative diagnosis was hermaphroditism, with the probability that the left gonad was intra-abdominal and contained ovarian tissue

Laparotomy—It was, therefore, with some degree of confidence that laparotomy was carried out On the right side of the pelvis there was no gonad and no internal genitalia On the left side there was a normal-sized ovary and fallopian tube and a unicornuate uterus The uterine body seemed to represent normal development of the left mullerian system, but, where the junction of the " body " and the cervix should have been, the uterus tapered away into a thickened cord which continued downwards to disappear beneath the bladder base The uterus, tube, ovary, and as much of the thickened cord as could easily be dealt with, were removed

Histological examination of these structures showed that the uterus had a normal muscle wall and was lined by a small amount of regenerative-type endometrium, the thickened cord had a fibromuscular wall and was lined by tall columnar mucus-secreting epithileum resembling normal endocervical tissue The architecture of the fallopian tube was normal The ovary contained one follicular cyst 2 5 cm. in diameter and a second smaller one, microscopically, numerous primary follicles were seen and there was one corpus albicans

Postoperatively the boy did well, and over the next few weeks there was an increase in the urinary output of gonadotrophins to 36 mouse units per day and a decrease in the output of œstrogens (to 20 I U daily) These findings presumably were related to the removal of the ovary, the rise in gonadotrophins being secondary to the fall in œstrogens

The patient was put on methyl testosterone 20 mg daily, and it is proposed continuing with this for some time Before his discharge from hospital, the father was told exactly what had been found and what had been done It was our opinion, and the father agreed, that the boy was completely oriented as a male, and he certainly fitted in well with the other members of the male adolescent ward on which he was nursed during his hospital stay The boy himself took all the surgical procedures with great calmness, and his main emotional reaction to it all was of delight at having got rid " of these things " from his chest wall

Blood-groups—Unfortunately, we could not make any attempt to establish mosaicism in this child, but the blood-groups were all established in detail and were as follows

A_1, MNS, P_1+ve, CDe/CDe, Lu(a−), K(a−), Le(a+b−), Fy(a−), Jk(a−), Wr(a−), C^W−ve Non-secretor

Family history—There was nothing of any great interest in the family history He was the eldest child of healthy parents who said no such thing had ever occurred before on either side of the family Next to him in birth order were twin boys aged 12 years, a boy aged 9 years, a girl aged 5 years, and a 2-year-old girl All the other children were said to be normal

Discussion

Clinical Features

When this boy first presented, the sound advice of Lewis (1959) had not been published This advice is that hermaphroditism should always be suspected in a boy with hypospadias and an undescended testis In the light of the present case this seems to be sound advice Whenever such a combination is encountered the sex chromatin should be determined

When our patient presented for the second time, it seemed probable, on clinical grounds, that he had Klinefelter's syndrome The hypospadias and the undescended testis, although not characteristically associated with this syndrome, could presumably occur with it Once the buccal smear showed that the patient was chromatin-positive, it seemed almost certain that the diagnosis was correct, although the results of the testicular biopsy were not available at that stage We had, however, established that the patient was a eunuchoid male with female distribution of pubic hair, absence of facial hair, primary microorchidism (Ferguson-Smith 1959), and considerable gynæcomastia on these features the preliminary diagnosis was made

Gonadal and Hormone Changes

Testicular biopsy certainly showed very considerable atrophy of the testis (Nelson 1956) Surviving tubules were lined solely by Sertoli cells and showed no spermatogenesis, other tubules showed varying degrees of intratubular fibrosis and collagen deposition The Leydig cells were reduced in quantity—a finding previously described in some cases of chromatin-positive Klinefelter's syndrome, although an increase in their number is more common

This absence of hypertrophy in the interstitial cells in the testis was compatible with the normal level of gonadotrophins in the urine since it is thought (Klinefelter et al 1942) that the hypertrophy is secondary to overstimulation of the Leydig cells by pituitary gonadotrophins as a response to the underproduction of the interal secretion of the Sertoli cells As was expected, the 17-ketosteroid excretion in the urine was perfectly normal for the patient's age, but the excretion of œstrogens was excessive for either a normal male or a patient with chromatin-positive Klinefelter's syndrome

The ovary on the other hand was well developed and of normal size Microscopically it showed primitive follicles and a corpus albicans, which indicated that ovulation had occurred It was structurally a much more active gonad than the testis

Operative Intervention

The initial operations on the hypospadias have been exceedingly successful and will enable the patient to lead a much more normal male life in the future, as will, of course, the complete bilateral mastectomy which he underwent. At the time of the mastectomy, the testicular biopsy and marrow puncture were performed so as to reduce the number of separate anæsthetics administered We were glad that it had been done that way, when eventually, as a result of the further studies, it became clear that laparotomy would have to be undertaken The condition found inside the pelvis was really quite striking, since on the right side there were no genitalia but on the left the ovary, tube, and left horn of the uterus were all present and of reasonable size The findings in this case bear out the suggestion of Jost (1953) that the development of the internal genitalia on each side may depend on the nature of the gonad on that side

The reasoning which lay behind the removal of all the female genitalia is more fully discussed later under treatment We all agreed that if female internal genitalia and an ovary were found, as we expected, then they should be removed in their entirety

Chromosome Analysis

This was perhaps the most important single finding in leading us away from the diagnosis of Klinefelter's syndrome, since it seems fairly certain that at least in all true cases of the chromatin-positive variety there will be an extra sex chromosome (either an X or a Y) so that the individual is genetically XXY Hitherto chromosomes have been counted mainly in known congenital malformations to find out if there is any abnormality of number or of gross morphology In the present case, however, it was used as a straight clinical investigation with most useful and revealing results

Treatment

It could be safely argued that this child was more female than male in that his sex-chromosome pattern was XX, his ovary was a much more adequately functioning organ than his testis, he had some uterine tissue, and he had pronounced breast development On the other hand, he was physically a male in general appearance and his external genitalia were masculine He had not even a vestigial vagina Most important of all, he was psychologically oriented as a male, and it has been strongly recommended (Marshall 1954, Hampson 1955, Money et al 1955, Wilkins 1957) that in these cases of intersex where the individual is not completely of either sex the patients should be brought up in the sex to which they have been accustomed and to which, superficially, they appear to belong In order to achieve this, it is necessary to remove the evidence of the other sex, so as to avoid embarrassment later on and, as far as possible, to leave the evidence of the obvious sex intact Since the whole future of the child is at stake, it is exceedingly important to make a firm decision at the time the child is under investigation and treatment (Lewis 1959), to carry out the treatment radically at the time and then to send the patient out into the world with the greatest possible security and confidence As with so many other things, it is doubts that may lead to trouble, and in the patient's mind these should be reduced as far as possible

Our thanks are due to Dr C C Bowley and Dr F I N Dunsford, of the Sheffield Regional Blood Transfusion Centre, for the detailed report of the patient's blood-groups, to Dr S Varadi, consultant hæmatologist, City General Hospital, Sheffield, for performing the marrow biopsy for the chromosome analysis, and to Dr C G Paine, consultant pathologist, Jessop Hospital for Women, Sheffield, for help with the histology and for supplying the photomicrograph

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Addendum

Since this article was submitted Ferguson-Smith et al (Ferguson-Smith, M A , Johnston, A W , Weinberg, A N ancet, 1960, ii, 126) have reported 2 cases of herma-hroditism and de Assis et al (de Assis, L M, Epps, D, ottura, C, Ferrari, I *Lancet*, 1960, ii, 129) have reported case in all 3 cases the normal basic diploid number of 6 chromosomes was thought to be present with an X constitution. Hirschhorn et al. (Hirschhorn, K, ecker, W H, Cooper, H L *Lancet*, 1960, ii, 319), owever, have described the case of an infant who is a ermaphrodite and who appears to be an XO/XY mosaic.

EXPERIMENTAL THYROIDITIS

AN APPRAISAL OF AUTOIMMUNE MECHANISMS IN ITS PRODUCTION

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Fromm et al (1953) noted that in patients with Hashimoto's thyroiditis the serum level of gammaglobulin was raised Others have reported positive results in colloidal-gold, thymol-turbidity, and cephalin-flocculation tests Roitt et al (1956) reasoned that the presence of lymphoid tissue and plasma cells in the thyroid lesion, together with these altered biochemical findings, suggested a disease of immunological significance They reported that sera from 7 of 9 patients with Hashimoto's disease gave a positive precipitin reaction when mixed with an extract from human thyroids In a later series (Doniach and Roitt 1957) 109 of 144 patients demonstrated this phenomenon.

About the same time, Rose and Witebsky (1956) reported the production in rabbits of antibody to injected homologous and autologous rabbit-thyroid extract mixed with Freund's adjuvant, and a histological alteration in their thyroids which resembled human Hashimoto's thyroiditis In a later series (Witebsky et al 1957), 32 of 35 rabbits showed thyroid lesions which to some degree paralleled the antibody titre Recently Terplan et al. (1960) summarised the findings in experimental thyroiditis in rabbits, guineapigs, and dogs While they noted a qualitative correlation between the demonstration of circulating antibodies and the production of thyroiditis in rabbits, no such correlation was found in either guineapigs or dogs, and even in rabbits there was no quantitative correlation between the titre of the antibodies and the severity of the thyroiditis

On the basis of these various reports a hypothesis for the pathogenesis of Hashimoto's thyroiditis was suggested (*Lancet* 1957) Some unknown mechanism, possibly related to the disruption of the follicular basement membrane which has been described in thyroiditis (Sommers and Meissner 1954, Stuart and Allan 1958), permits the localised release of thyroglobulin from the thyroid follicles The presence of colloid material in the interfollicular connective tissue has been demonstrated by the fluorescent-antibody technique (White 1957) In response to this extravasation, an inflammatory reaction quickly develops, with the plasma cells producing antibody to thyroglobulin The resultant antigen-antibody reaction causes more follicular damage and increased leakage of colloid Excess colloid eventually enters the circulation, producing a generalised antibody response On this hypothesis Hashimoto's thyroiditis would be classified as a self-perpetuating autoimmune disease—one end-result being destruction of the thyroid with associated myxœdema

We have re-examined some aspects of this hypothesis First, some of the work of Witebsky et al has been repeated in an effort to reproduce ' immunological " thyroiditis, and in these experiments the antibody titres of the animals have been followed serially Secondly, an attempt has been made to simulate the theoretical spillage of thyroglobulin into the circulation by giving rabbits repeated intravenous injections of thyroid extract and following their antibody production. Thirdly, a pilot study has been done to ascertain the possible effects of local trauma to the thyroid gland on antibody production.

Methods

Thyroid extract was prepared according to the method of Witebsky et al (1955) Thyroids from healthy rabbits were dissected free of fat and connective tissue and frozen on dry ice. The frozen glands were homogenised in a 'Teflon' grinder and extracted with cold isotonic saline for twelve hours The supernatant, after centrifugation at 3000 r p.m for five minutes, was emulsified with equal volumes of Freund's adjuvant.‡ Three experimental procedures were set up

Experiment I

One group of 18 rabbits was given thyroid extract and Freund's adjuvant containing 0 5 mg of *Mycobacterium butyricum* ‡ per ml A second group of 15 rabbits received the mixture containing 2 5 mg of bacteria per ml This latter concentration only slightly exceeded that used by Witebsky The rabbits (weighing 2500 g equally sexed) were given 0 05 ml. of the above emulsified antigens into each foot pad Antibody titres were estimated by the tanned-red-cell technique of Boyden (1951) as modified by Stavitsky (1954) Titrations were done at approximately three-weekly intervals on the day after bleeding The sera were then frozen and re-examined when the animal was killed. At this time all the sera from each animal were tested on one day No significant differences were noted after long storage. Sera were also tested against different batches of antigen without any significant variation in titre

Experiment II

12 rabbits were injected intravenously with the saline thyroid extract alone, they received 0·025 ml. (diluted to 0 1 ml.) every two days for four weeks 2 additional rabbits were given 0 1, 0 2, 0 4, 0 6, and 1 0 ml of thyroid extract every three days All these injections were given into the marginal ear vein. Hæmagglutination titres were estimated every six weeks, and the animals were killed after seven months

Experiment III (Pilot Study)

Physiological saline and Freund's adjuvant with both low and high bacterial concentrations were injected into the right lobe of the thyroid, a separate rabbit being used for each material Hæmagglutination estimations were done every two weeks and the animals killed at eight weeks when the right and left lobes were dissected and fixed separately in formol saline.

Results

Experiment I

7 of the 18 rabbits which had received the lower bacterial concentration in the Freund's adjuvant exhibited antibody against the thyroid extract. 2 of these rabbits, which displayed a prompt response with titres above 1/4000 at six weeks, were killed three months after initial injection, when the titre was still higher One of these showed a few focal collections of lymphocytes and plasma cells in the thyroid gland associated with slight follicle damage (fig 1) 2 further rabbits were killed at six months when the antibody response suggested a maximum. The immunological response of one is shown in fig 2. In the series of Witebsky, titres of this level were usually

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† Lederle Medical Student Research Assistant

‡ Difco Laboratories, Detroit, Michigan.

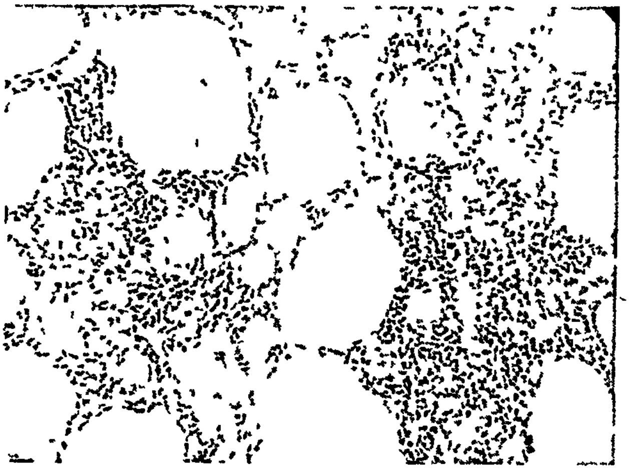

Fig 1—The only focal area of thyroiditis observed in 1 of the 15 rabbits that developed hæmagglutinating antibodies This was the only focus of inflammation in the entire gland (×245 Hæmatoxylin and eosin)

associated with considerable histological change in the thyroid gland, but in neither of our animals were any unusual features seen The last 3 animals were followed for one year, and their antibody titres, after reaching a maximum at three to five months, fell gradually (fig 3) to reach normal (1/16) by eight months No changes were seen in the thyroids when the animals were killed at twelve months No thyroid damage was seen in the animals which had shown no antibody response

11 of the 15 rabbits receiving the higher concentration of *Myco butyricum* in Freund's adjuvant developed circulating antibody against thyroid extract 8 of these still showed a significant titre, ranging from 1/128 to 1/4000 when they were killed seven months after inoculation No significant pathological lesions were found in the thyroids of any of this group, except for a few small foci of lymphocytes in 3

Experiment II

The rabbits given intravenous injections of thyroid extract showed neither antibody response nor any histological alteration of the thyroid gland

Experiment III

The injection of saline and Freund's adjuvant into the right lobe of the thyroid had a conspicuous local effect The gland injected with saline showed a dissolution of the follicular walls with spillage of colloid into the interfollicular tissues, while those that had been injected with the Freund's adjuvant showed complete destruction of the gland architecture and an associated chronic granulomatous reaction with abundant plasma cells and lymphocytes, and some multinucleated giant cells

In spite of this extensive local thyroid damage, no circulating antibodies were demonstrated in the animals and no pathological lesions could be demonstrated in any of the contralateral thyroid lobes

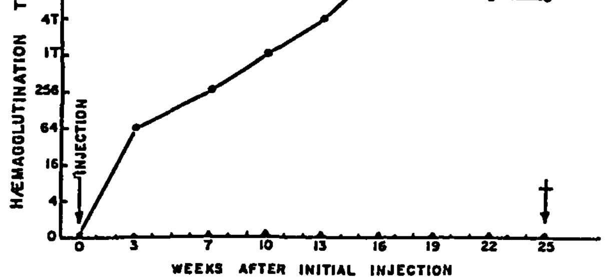

Fig 2—Serial hæmagglutination titre of rabbit showing maximum of 1/32,000 at four months and 1/8000 at six months when animal was killed (The second rabbit had a maximum of 1/8000 falling to 1/4000 when killed)

Discussion

In this experiment on rabbits we have been able to produce, fairly regularly, antibodies against saline thyroid extract when the antigen is emulsified with Freund's adjuvant The number of animals in which this could be accomplished was related in part to the concentration of the mycobacterium in the adjuvant The antibody curve was that which could be expected after a single antigenic stimulus There was no evidence that the immunological reaction was being perpetuated

No lesions were produced that remotely resembled Hashimoto's thyroiditis Occasionally small focal collections of lymphocytes were observed, but they were not associated with any follicular alteration and were not considered significant except in one possible instance (fig 1)

When no adjuvant was used and the saline antigen was injected intravenously no antibody could be demonstrated, although the quantity injected exceeded many times the maximum volume extracted from the thyroid gland of one rabbit Neither were any thyroid lesions produced Local severe damage to a single lobe of the thyroid produced neither circulating antibodies nor any lesions in the contralateral lobe

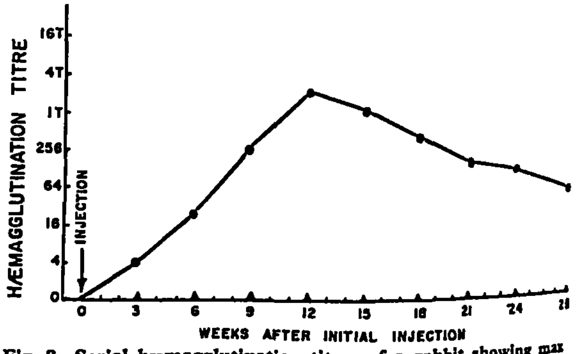

Fig 3—Serial hæmagglutination titres of a rabbit showing maximum response at three months with a gradual decline (The other 2 rabbits showed similar curves All reached 1/16 by eight months)

The antibodies demonstrable by the hæmagglutination technique in the sera of most patients with Hashimoto's thyroiditis may be a reflection of the pathological change rather than its cause It has been shown that these antibodies are directed only against the thyroglobulin moiety of the crude thyroid extract

Trotter et al (1957), Belyavin and Trotter (1959), and Anderson et al (1959) have shown that a second antigen antibody system exists in many of these patients and can be demonstrated only by the complement-fixation reaction In this system the antigen appears to be an intracellular component, being recovered in the "microsomal" fraction of thyroid homogenates The highest concentration of this antigen is found in thyrotoxic thyroid glands It is possible that damage to the thyroid, resulting from an intracellular antigen-antibody reaction involving this system, might be the initiating factor of thyroiditis, and that leakages of antigenic thyroglobulin may then lead to the formation of antibody so readily demonstrated by the hæmagglutination techniques It seems very doubtful that this latter circulating antibody plays any particular role in compounding further thyroid damage by antigen-antibody union within the acini One must also recognise the possibility that some other cytotoxic agent may be involved, as suggested by Pulvertaft et al (1959) and Irvine (1960)

Our failure to produce thyroid lesions in the rabbit may have been related to the nature of the antigenic material derived by saline extraction from normal thyroids Since there is some clinical evidence that thyrotoxicosis may precede certain forms of thyroiditis, we are now trying to assess the effect of antigens prepared from experimentally produced hyperplastic rabbit thyroids and antigens prepared by methods other than saline extraction

Summary

Circulating antibodies, demonstrated by the hæmagglutination technique, have been produced readily in rabbits by injecting them with a homologous antigen obtained by saline extraction of thyroids emulsified with complete Freund's adjuvant However, no significant lesions were observed, nor were antibodies or lesions produced in other rabbits given the saline extract antigen intravenously Direct injury of one thyroid lobe failed to produce hæmagglutination antibodies or lesions in the contralateral lobe

These findings cast considerable doubt on the importance of the hæmagglutinating antibodies in the initiation of thyroiditis or in their compounding further thyroid damage by a self-perpetuating autoimmune mechanism

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NICKEL SENSITIVITY AS A CAUSE OF INFUSION REACTIONS

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MANY of the cannulæ used for routine intravenous infusions either are nickel-plated or are made of a nickel-containing alloy In this country alone, many hundreds of infusions are given via such cannulæ daily, but nickel dermatitis from this cause has not been described The following cases, which were seen in one hospital within three months, suggest that this reaction can occur

Case-records

Case 1 —A married woman of 35 was admitted for bilateral breast reduction. Her history and the physical examination revealed no abnormality apart from the large breasts After induction of anæsthesia a plasma infusion was set up, and the patient was placed on the operating-table in a semi-sitting position, with a 20° head-up tilt 30 minutes later her condition began to deteriorate, and after a further 15 minutes, her systolic blood-pressure was only 40 mm Hg Blood, dextran, and finally noradrenaline were given before her condition improved Only one breast was operated upon because of this incident, and an infusion was continued for about 7 hours after the operation

Next day, she was quite well, but a generalised urticarial rash with pruritus developed and persisted for 5 days, despite treatment with anti-histamine drugs Apart from the rash, she made a good recovery and was discharged home on the 17th postoperative day

When the rash appeared, the patient told the ward staff that she was nickel-sensitive, but it was not appreciated that she had been in contact with nickel, and the importance of this information was overlooked

The same patient was admitted 10 days later for operation on the other breast The course of this operation was uneventful It was performed with the patient supine and after premedication which included the anti-histamine drug promethazine She was given two pints of blood during the operation, and the infusion was continued for 4 hours after the operation

On the second postoperative day, a generalised urticarial rash again developed and persisted for 2 weeks It was associated for part of this time with angioneurotic œdema of the face and upper limbs She was discharged on the 21st postoperative day

Case 2 —A married woman of 23 was admitted as an emergency with a perforated duodenal ulcer She was given two bottles of plasma before the operation, and a pint of blood during the operation, and intravenous therapy was continued for a further 48 hours About 8 hours after the operation, she began to feel itching and paræsthesiæ in her hands and feet, but she said nothing about this at the time

On the first postoperative day, a generalised erythematous rash developed, with small vesicles around the nail-beds of her fingers and toes She was asked about previous skin rashes, and she said that her doctor had told her she had nickel dermatitis, because she had a local reaction if she wore underwear with metal buckles, or costume jewellery, particularly earrings

When the infusion was stopped next day, a localised urticarial weal was found corresponding with the exposed part of the hub and shaft of the infusion cannula This was surrounded by an area of erythema which almost encircled the arm and which itched intensely The rash subsided in about 5 days, but on discharge from hospital on the 8th postoperative day, the patient still complained of itching between her fingers and toes, and had some minute petechiæ on the palms of her hands

Investigations

The two types of cannulæ and the metal gauze filter in infusion sets in this hospital, and the cannula in the Capon Heaton disposable infusion set were analysed

Cannula 1 (obtained locally) —Nickel-steel shaft, brass hub, nickel-plated

Cannula 2 (obtained from the Ministry of Health) —Nickel-steel shaft, brass hub, nickel-plated

Cannula 3 (Capon Heaton) —Nickel-steel shaft, plastic hub

Metal gauze filter —Nickel 66%, copper 34%

To confirm that these cannulæ could cause sensitivity reactions, a subject known to be nickel-sensitive was patch-tested with cannulæ 1 and 2 The cannulæ were removed after 24 hours, and 12 hours later, a local eczematous reaction occurred, with erythema, small vesicles, and pruritus At the same time, the subject became sensitive to the metal parts of her underwear, and developed a reaction at each site

No history of sensitivity to substances other than nickel could be elicited from either of the above-mentioned patients Dr G Holti, of the department of dermatology, was provided with a list of the substances the patient in case 1 was known to have been in contact with immediately before, during, and after the operations The list did not include nickel, but included thiopentone, penicillin, streptomycin, cetrimide, 'Phisohex', 'Raytex', 'Hibitane', black silk, and catgut Negative findings were obtained with all except intradermal cetrimide 0 5%, and Dr Holti was of the opinion that this positive reaction was of doubtful significance, because there was no reaction where the patient's skin was prepared with cetrimide immediately before the operation

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This patient was later tested for sensitivity to nickel A prick test with 1% nickel sulphate produced a 4 mm urticarial weal within 15 minutes This reaction disappeared during the next hour, but four hours later there was a secondary reaction at the site of the prick test in the form of an urticarial weal, the size of a sixpence (2 cm), with a "tadpole tail" of œdematous lymphatics leading from it This reaction was subsiding when the patient went to bed 4 hours later and had disappeared by the next morning, but there was an easily palpable thickening at the site of the prick test 48 hours later A patch test performed with 1% nickel sulphate produced a local eczematous reaction after 48 hours

Discussion

Nickel dermatitis is an acquired sensitivity reaction It was the commonest contact dermatitis in the large series of Marcussen (1959), and its incidence is thought to be increasing (Calnan 1956, Fisher and Shapiro 1956, Marcussen 1959)

Because they are more often in contact with this metal than men, women are more commonly affected The metal is present in most plated objects and in many alloys, however, and men may also acquire sensitivity to it

Nickel dermatitis is characterised by a primary eruption at the site of contact, which may be followed by spread to other sites, such as elbow flexures, face, and eyelids Generalised spread usually takes the form of an eczematous eruption, but angioneurotic œdema, erythema multiforme, urticaria, pruritus, or prurigo may develop (Calnan 1956) If circulating antibodies are present, an anaphylactoid reaction is possible (Holti, personal communication)

Allergic reactions to blood or plasma are said to arise in from 1% (Maunsell 1944, Hoxworth and Skinner 1941, Seldon 1956) to 3% (Stephen et al 1956) of infusions Maunsell concluded that this type of reaction was due to sensitivity of the recipient and not to the blood or plasma infused Discombe (1958) stated that allergic reactions arose in from 2% to 8% of infusions, and he described an anaphylactoid non-hæmolytic reaction of unknown cause

The cases described may be regarded as examples of nickel sensitivity, the generalised spread being due to the introduction of nickel into the circulation In one patient, there was also a typical local reaction In the other patient, this was not looked for The collapse of the first patient may have been an anaphylactoid reaction to nickel, and the immediate reaction to the prick test makes this probable There are, however, other possible causes for this episode—particularly reduced venous return due to the patient's position Electrocardiography, chest X-ray, urine microscopy, and spectroscopy were normal

Perhaps the most likely alternative cause of the rashes in these cases is an allergic reaction to the blood or plasma infused, and this cannot be excluded There was no evidence of incompatibility, however, with the blood infused Reactions to blood or plasma usually take the form of rigors and pyrexia, if skin reactions occur, they usually do so either during the infusion or within 2 hours of it, and do not persist for more than 6 hours (Maunsell 1944, Stephen et al 1955, Griffitts and Elliott 1955, Seldon 1956, Discombe 1958) If the collapse of the first patient is disregarded, the first symptom of a reaction did not occur until 8 hours after the blood transfusion was stopped, in the other case, the interval was 18 hours on the first occasion, and 36 hours on the second occasion

Summary

Skin reactions developed in 2 patients who had had infusions, and in 1 of these there was also an alarming anaphylactoid reaction It is suggested that the cause was sensitivity to the nickel in the infusion cannulæ As nickel sensitivity is relatively common, a proportion of the hitherto unexplained infusion reactions may be due to nickel cannulæ, which may produce manifestations of the immediate or delayed type of hypersensitivity

I wish to thank Dr G Holti for his very helpful advice, and for performing the skin tests on the first patient I should also like to thank Dr J A Gilchrist, of the department of metallurgy, King's College, Newcastle upon Tyne, for performing the analyses, Dr M H A Davidson and Dr D C C Stark for referring case 1 to me, and Prof E A Pask and Prof C A Green for their encouragement

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FATAL RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

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DEFECTS in the cuffs of endotracheal tubes are occasional cause of respiratory obstruction Incid described include the herniation of part of the cuff c the open end of the tube (Forrester 1959) and herniat of the cuff into the lumen of an armoured tube (Rob and Pearce 1959)

We now report another possible mechanism und lying this type of accident

Case-report

A healthy woman, aged 33, was admitted to hospital for removal of a moderate-sized, non-toxic, nodular go X-rays of the chest and neck revealed no evidence of trac displacement or narrowing

Premedication was with 10 mg morphine and 0 6 atropine one hour preoperatively

Anæsthesia (A F W)—Induction was with thiopent sodium 375 mg and succinyl choline 70 mg The lungs w inflated with oxygen, the vocal cords and trachea were spra with 4 ml. of 4% lignocaine, and the patient was then intubated with a no. 8 Magill cuffed endotracheal tube. The cuff was inflated immediately before use, and appeared to be in good condition. Following intubation, the cuff was again distended with air from a syringe. Filling was judged to be adequate when leakage of air past the cuff just ceased on inflation of the lungs. Anæsthesia was maintained with nitrous oxide and oxygen (6.2 litres per minute) on a semi-open circuit, and respiration was controlled. Full spontaneous respiration returned after a few minutes, and the patient was then transferred to the operating-theatre.

Infiltration of the superficial tissues in the operation field was carried out, using 80 ml. of a solution containing 400 mg. lignocaine and 0.5 mg. adrenaline in 160 ml. of physiological saline. Before the incision was made the patient was given 15 mg. of tubocurarine chloride, and thereafter respiration was assisted.

The operation (R. R. L. P.) proceeded uneventfully until the point when the partial resection of both lobes of the thyroid was about to start. At this moment the anæsthetist was suddenly unable to inflate the lungs. Thinking that the tube might have become incorrectly placed, she adjusted its position, with no result. All surgical instruments were removed from the wound to exclude the possibility of tracheal compression at this site. Head towels were then removed, revealing that the patient was deeply cyanosed. Laryngoscopy was performed, and kinking of the tube excluded. The cuff was deflated, and a suction catheter was passed, and, although no mucus was obtained, the airway was restored after this manœuvre.

At this juncture the lungs were inflated with pure oxygen, without improvement in the patient's colour. The pulses were examined, but could not be felt, and the pupils were found to be widely dilated.

An intracardiac injection of adrenaline was given, without effect.

Transthoracic cardiac massage was performed through an anterior incision in the fifth left intercostal space. The heart was found to be arrested in diastole. After 30 seconds of massage, contractions began, and normal rhythm returned rapidly. Inflation with oxygen was continued throughout this period, and, with the return of the pulse, the patient's colour reverted to normal. 20 minutes later the pupils had contracted symmetrically, and shortly afterwards spontaneous respiration restarted. The blood-pressure remained low, but recovered after infusion of 540 ml. of 'Intradex' (6% dextran in physiological saline). Thyroidectomy was then completed, after which the thoracotomy incision was closed. At the end of the operation the patient was returned to the ward.

Postoperative course.—At this time, respiration was full and spontaneous, and the pulse, colour, and blood-pressure seemed satisfactory. The patient appeared lightly unconscious, making crying noises, and apparently resenting painful stimulation. Twitching movements of her face were noted.

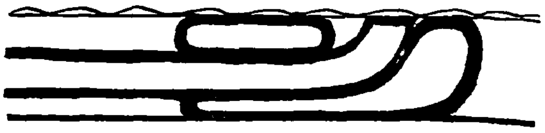
During the next 6 hours the level of unconsciousness slowly deepened, twitching of the face and limbs became more prominent, and the pupils dilated progressively. As these signs indicated anoxic cerebral damage, measures were taken to combat the associated cerebral œdema. Intravenous administration of 50% sucrose (Argent and Cope 1956) and concentrated plasma, with pressor drugs (methylamphetamine and methoxamine), failed to produce any notable effect, and the patient died in coma 6 hours after leaving the theatre.

The Endotracheal Tube

After the operation one of us (D. L. P.), who had been in an adjacent theatre, and had been sent for when the respiratory obstruction developed, examined the endotracheal tube and found that the cuff inflated unevenly. There was an obvious localised balloon-like protrusion which had developed at a presumed point of weakness in the most distal part of the cuff. This was located on the aspect of the cuff which lay behind the bevel of the tube. As the tube was known to be normal when inserted, the possibility was considered that this protrusion had occurred during the operation, and had forced the bevelled open end of the tube against the tracheal wall, thereby occluding the airway.

Necropsy (Dr. H. J. Harris).—This showed the cause of death to be cerebral anoxia due to respiratory obstruction and cardiac arrest.

At the postmortem examination, the endotracheal tube used for the anæsthetic was inserted, with the patient's body placed in the extended-neck position adopted at operation. By opening the trachea longitudinally, it was possible to observe the exact position of the tube. It was found to be correctly placed, with the tip 1 in. above the carina. The open bevelled end was observed to face anteriorly. Inflation of the defective cuff resulted in the open end of the tube being forced firmly against the front of the trachea (see figure). The appearances suggested to those present that this would have resulted in complete obstruction of the tube at operation.



Diagrammatic representation of findings at necropsy experiment.

Comments

We make the following comments after considering the episode described.

1. Uneven inflation of cuffs, as a result of weakness in the rubber or perishing during storage, is found fairly frequently when large numbers of stored tubes are examined. In the operating-theatre where the episode described here took place, all endotracheal tubes are examined, and the cuffs inflated weekly by the theatre superintendent, faulty ones being rejected. In addition, each tube is inflated and tested by the anæsthetist before use. Despite these precautions, it was possible for a defect to develop suddenly, while the tube was in use, with the results described. This emphasises the importance of discarding any tube where the least suspicion of weakness or uneven inflation exists.

2. It is understandable that, where an anæsthetist employs an endotracheal tube with the express purpose of avoiding respiratory obstruction, he may fail to consider that a defect in the device itself may produce the very complication that he seeks to avoid. Should obstruction develop, he is likely to consider other possibilities first. As this incident shows, such delay may prove fatal. We therefore draw attention to this possibility, and suggest that, where possible, immediate or early deflation of the cuff should be practised in such circumstances.

3. It is often stated that, when cardiac arrest occurs, a period of about 4 minutes elapses, at room-temperature, before irreversible anoxic damage takes place in the brain. Some have suggested that part of this period may be spent in attempting less radical measures to restore the heart action, before undertaking cardiac massage. But many would dispute the advisability of any immediate measure short of cardiac massage.

Where cardiac arrest is secondary to respiratory obstruction, the brain is already anoxic, and the assumption that any safe margin of time exists is invalid. No time should be lost in starting cardiac massage, as this is undoubtedly the most effective way of restarting the pulse.

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Reviews of Books

Intussusception in Infants and Children

MARK M RAVITCH, M D , associate professor of surgery, Johns Hopkins University School of Medicine, and surgeon-in-chief, Baltimore City Hospitals Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 119 76s

THIS monograph is based on twenty years' experience with the reduction of intussusception by hydrostatic pressure in the Harriet Lane Home of the Johns Hopkins Hospital It is clear from the figures Dr Ravitch gives that intussusception is probably more common in some of the pædiatric surgical centres of Great Britain and Europe than in those of the United States In the Harriet Lane Home 199 intussusceptions have been treated between 1893 and 1958 and the mortality has fallen from 75% to nil in the years 1948 to 1958, while the average duration of symptoms has fallen from fifty-six hours to twenty-five hours in the ten years up to 1958 From 1893 to 1948 only 4 children died out of 52 treated within twenty-four hours of the onset of symptoms In 1876 Hirschsprung of Copenhagen reported the use of hydrostatic pressure in the treatment of 107 patients with intussusception with a mortality-rate of 35% when the general mortality from the disease was 80%, in the 84 cases he treated with enemas alone the mortality was 23% In 1926 Hipsley of Sydney was able to report 100 patients treated by saline enemata with only 5 deaths Between 1939 and 1957 reduction by barium enema has been attempted by the Harriet Lane Home in 77 patients and has succeeded in 53, but operation was judged advisable in the remaining 24, in 5 of whom the intussusception was found to be reduced completely, and in 18 it has been pushed back to the cæcum Reducibility by enema was not related to the position of the apex at the time of diagnosis None of these 77 patients died

There is a good description of the technique of reduction by enema and of the precautions which should be observed It is obvious that a limit must be set to the duration of the procedure and while some intussusceptions may be reduced in a few minutes others may persist even after three-quarters of an hour The image-intensifier is likely to make this method of treating intussusceptions more readily applicable than before and the results of this method in some centres in North America and Australia clearly demand respect There are few hospitals in this country which have achieved such low mortality-rates by operation alone and it seems as if surgeons and especially pædiatric surgeons must think again about their methods of treating intussusception—and they should all read this book

Safe Handling of Radioactive Isotopes in Medical Practice

EDITH H QUIMBY, SC D , professor of radiology (physics), College of Physicians and Surgeons, Columbia University New York New York and London Macmillan Company of New York 1960 Pp 129 31s 6d

OFFICIAL codes of practice governing the use of radioactive isotopes in hospitals in this country and in the United States and the guide issued by the International Atomic Energy Agency all prescribe the appointment of a radiation protection officer who is expected to draw up detailed working rules for his hospital and to deal with day-to-day difficulties or emergencies Professor Quimby seeks to ease his task by providing enough background information to enable the people concerned, notably technicians and nurses, to appreciate the reasons for the detailed rules which they are expected to follow

Introductory chapters on radioactivity and its measurement, the nature of radiation hazards with particular reference to isotope work, and the main clinical uses of radioactive materials, deal briefly with their complex subject matter yet remain readable, clear, and informative Other chapters describe in detail various practical problems, illustrated where appropriate with numerical examples The radiation protection officer himself will find it a practical reference book when dealing with queries which may lie outside his own experience With the help of the excellent index he can, for instance, quickly find the answer to such questions as the possible hazard to the fœtus if a pregnant nurse is looking after a radioactive patient or the possible risks faced by the "funeral director" who may be dealing with a radioactive corpse It will also be a useful guide for anyone who has the difficult task of giving some elementary lectures on this subject Indeed, Professor Quimby has succeeded so well in presenting a great deal of information in a form which can be understood by a non-specialist that it is particularly unfortunate that the price of her small book is so high as to put it out of the reach of most of the people for whom it is intended

Diseases of the Newborn

ALEXANDER J SCHAFFER, M D , associate professor of pediatrics, Johns Hopkins Medical School, pediatrician to Johns Hopkins Hospital Philadelphia and London W B Saunders 1960 Pp 878 140s

THE medical management of the newborn is challenging and exciting—challenging because of the variety of disorders met in this hazardous period, and exciting because the physical status of the patient is unknown until the first examination Dr Schaffer writes with the interest and enthusiasm of one who has accepted the challenge and felt the excitement With the exception of the section on cardiac disease (by Dr M Markowitz), it is a personal book and is all the better for that

He puts the emphasis on diagnosis and treatment and does not wander down the pathways of fœtal and neonatal physiology unless he is clinically compelled to do so The authority of the book derives from his wide experience and selective reading and his rich gathering of illustrative cases Though his book is not encyclopædic he describes helpfully most conditions affecting the newborn The balance between rare and common conditions is more suitable for the practising doctor than the medical student The references, mostly from American or British sources, have been sensibly chosen from among the readily available rather than the most academic

One day a multi-authored, comprehensive, and probably unreadable book will appear on the newborn infant Some pædiatricians and some libraries will prefer it, but Dr Schaffer need have no regrets, for his book, which he has obviously enjoyed writing, will already have won its own permanent place

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Relaxation for Childbirth. (London Heinemann Medical Books 1960 Pp 148 12s 6d)—Instruction in controlled relaxation during labour has helped many mothers both physically and mentally, not only during childbirth itself but also during pregnancy and later Miss Mary Barfield found her courses of instruction to expectant mothers so successful that she thought her methods might help others out of reach of classes—so she wrote this book She has chosen to write just as she speaks to the mothers, and the result often seems rambling, making it difficult to look anything up But anyone who is undaunted by this will find here, with one omission, the important details about relaxation in childbirth The omission is a discussion of the vital difference between attending a course in "natural childbirth" and reading a book about it Relaxation during labour is extremely hard for most women to achieve even those who can relax easily under normal conditions often find it impossible in the presence of extreme discomfort (in the language of "natural childbirth" the word "pain" is not allowed) There are a few lucky women to whom relaxation during childbirth comes naturally, either with or without training, but most Western women require long training, attendance at classes, and often the devoted services of an expert during the actual labour Such women are unlikely to be successful simply from reading a book Miss Barfield's text contains many ecstatic descriptions of motherhood, but it does not discuss the less radiant side of the picture Women who suffer a lot despite or even because of "training" in relaxation may not let Miss Barfield know how they feel—but they have plenty to say to the doctor who attends them

THE LANCET

LONDON 1 OCTOBER 1960

Perchance to Dream

In olden times dreams and their interpretation played a large part in statecraft, and the decline in such use has left our political scene the duller Latterly the classic work of **Freud**[1] on dream interpretation, first published some sixty years ago, laid the foundations of psychoanalysis; and, with a different approach, J W **Dunne**,[2] the philosopher and mathematician, used dreams for time experiments **Dunne's** conclusion that subsequent events could be recognised in preceding dreams was based on a good deal more evidence than is often realised with the rise of extrasensory perception as a respectable subject, his careful work merits a second look Unfortunately, owing to the subjective, elusive, and unrepeatable nature of dreams, scientific control of their investigation has proved difficult, though **Eysenck**[3] reported an interesting technique an imaginary episode, implanted in a volunteer under hypnosis and banished to posthypnotic amnesia, was followed by a very relevant dream packed with Freudian symbolism

A new and promising line has been opened up by **Dement**,[4] of Mount Sinai Hospital, New York Starting from the observation that dreams were accompanied by rapid synchronous eye movements (probably as the dreamer "watched" the events of the dream) he studied dream cycles by means of electroencephalograms (E.E.G) and electrical records of eye movements A typical night of undisturbed sleep was found to include four or five periods of dreaming, each lasting some twenty minutes and accompanied by lightening of sleep, shown on the E E G In an effort to establish how far this dream experience (equal to about 20% of the total sleep-time) was physiologically necessary, dreaming was abolished for five successive nights as soon as eye movements and E.E G s suggested the start of a dream cycle, the eight volunteers (all were young men) were firmly woken up On the first night this awakening was followed by a normal dreamless spell, but the pressure of dreaming increased and more and more frequent awakening was required on subsequent nights Practical difficulties prevented total dream deprivation, and **Dement** estimates that the dream loss was 65–75% During the first of the subsequent "recovery" nights of undisturbed sleep, six of the eight volunteers dreamed some 50% in excess of normal, one subject dreamed normally on the first recovery night (after a cocktail party) but excessively on the following four nights, only one did not over-dream Compensatory over-dreaming lasted for about five nights—i e, about the same time as the preceding deprivation. That this result was due to deprivation of dreams rather than of sleep was suggested by a further series of recordings in which six of the subjects were similarly awakened for the same number of nights but not during dreams thereafter the increase in dream-time was much smaller During dream deprivation the subjects became anxious and irritable and their mental concentration poor one subject left the study in apparent panic after three nights and two others stopped short at four nights, five had a greatly increased appetite and gained weight. All these changes disappeared when the dreaming was restored There were no such changes during the "control" awakenings The volunteers for this study must have reflected that Macbeth was not the only one who murdered sleep

These results would have been no surprise to **Freud**, who held that "dream-work" was a vitally important part of mental function An impressive case has been made for regarding dreaming as a basic human need More important **Dement** has evolved a new technique for the study of the mind which opens a long row of doors Physical and mental illness, drugs, personality, age, sex, and cultural background are obvious variables to be correlated with dream patterns, and this work may lead to really valid means of analysing dream content.

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Diagnosis of Diabetes

At present diabetes mellitus is usually diagnosed when the patient reports with symptoms due to the primary disorder or, in about 20% of cases, to complications of the disease[1] Less commonly cases are discovered incidentally by routine testing of the urine **Reid**[2] found that 48% of 352 diabetics he studied in Dundee had had symptoms continuously for more than four months when they were diagnosed and 20% had had symptoms for more than a year Such a state of affairs would no longer be tolerated for tuberculosis, and should no longer be tolerated for diabetes In tuberculosis infectivity is an important factor, but delay in the diagnosis of diabetes can be serious enough It involves needless suffering and impaired efficiency which may cost the patient his job, increases the severity of the diabetes, and favours the development of complication such as cataract. Some of the delay in diagnosis is doubtless due to imperfections in the practice of doctors who fail to test the urine when the clinical picture suggests diabetes, but much is due to ignorance among the lay public There is a widespread tendency to misinterpret the symptoms of this disease Polyuria and visual impairment, for instance, may be regarded as inevitable concomitants of senescence, and loss of weight may be welcomed, particularly by the obese postmenopausal women in whom diabetes is especially liable to develop in **Reid's** series long delay in diagnosis was about twice as common in women as in men Thirst may sometimes be credited with a healthy significance, and pruritus vulvæ may not be mentioned because of embarrassment Reid revealed the depths of lay ignorance about diabetes in a pilot survey of 250 people attending a chest clinic, who were asked to fill in a simple questionary 78% could express no opinion about the cause of diabetes, and 28% were not sure whether or not it was infective 69% did not know one symptom of diabetes or of its complications, and only 5% knew two or more symptoms 28% did not know whether or not treatment of diabetes is successful—a fact relevant to the delay in reporting symptoms when their significance is recognised The little knowledge of diabetes in this group was derived mainly from conversations with diabetic relatives or acquaintances rather than from reading, the radio, or television

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[1] Beaser S B *New Engl. J Med* 1948 229, 765

[2] Reid, J J A. *Med. Offr*, 1960, 103, 325

A resolute effort is needed to lessen this ignorance Since 1–2% of the population are diabetic [3]—about half of them unknowingly [4]—it seems reasonable that simple instruction in the symptoms of the disease and their significance should be given not only through mass media of publicity but as part of instruction in biology in schools This disease can now be diagnosed in the latent phase or even earlier—that is, in the prediabetic phase If the doctor recognises clinical pointers to the disease, then latent diabetes may be revealed by tests of carbohydrate tolerance, and if such tests are at first normal, prediabetes may be revealed by their repetition after administration of cortisone or other glucocorticoids [5–7] Clinical pointers include a strong family history of diabetes, especially in the elderly and obese, transient glycosuria during stress, the production of excessively large babies or stillborn babies with hyperplasia of the pancreatic islets, and repeated miscarriages or toxæmia of pregnancy, excessive maternal weight-gain during pregnancy often associated with excessive lactation, or congenital malformations in the offspring [8] By such means the diagnosis of diabetes may be made to antedate by many years the appearance of the overt disorder In this phase correction of obesity [9] and possibly administration of hypoglycæmic sulphonylureas to stimulate hyperplasia of the insulin-producing β-cells of the pancreatic islets [10] may do much to delay or avert frank diabetes

Cyclical Œdema and Shock

Increased permeability of the capillary wall to plasma-protein is a common cause of local œdema in inflammatory and allergic states, but generalised œdema due to loss of protein through the walls of capillaries throughout the body must be extremely rare Leakage of protein through the capillaries of particular organs (as in the protein-losing kidney [11] or protein-losing gastro-enteropathy [12]) produces effects which are drastic enough, but when such losses take place throughout the body they must cause not merely a hypoproteinæmic œdema but profound and dangerous oligæmic shock From New York we now have a report,[13] remarkable both for the rarity of the circumstances and the thoroughness with which they were investigated, of a patient who had many episodes of œdema associated with shock, the last of which proved fatal

A previously healthy married woman of 32 had an attack of generalised swelling, associated with nausea and vomiting, which lasted for a few days Similar attacks recurred after intervals of 5 and 8 months, but thereafter they became more frequent, and 20 attacks were observed over a 2-year period In a typical severe attack with shock, of which there were nine, the onset was with malaise, chilliness, and a temperature raised to 39 3°C (102 7°F) The blood-pressure fell from normal levels to 30/0 mm Hg, and could be raised by amounts of plasma ranging from 500 to 3300 ml Clinically detectable œdema was present in only some of the attacks, but in all of them the patient gained several kilogrammes in weight Death in the last attack was sudden, and at necropsy the lungs were œdematous, but there was no embolism The attacks were related in time to the menstrual cycle, usually just preceding the menstrual flow but occasionally starting a day or two later This time relation was so striking that after several life-threatening attacks the uterus and later the ovaries were removed Thereafter the frequency of attacks decreased only temporarily

Many investigations were made, some were directed towards showing that the attacks were associated with widespread increase in capillary permeability (these were unequivocally positive), others were directed towards finding the cause of the abnormal permeability (these yielded no definite conclusion, but ruled out several reasonable hypotheses) There is the circumstantial evidence that the hæmatocrit percentage was increased in the attacks, during which the infusion of plasma raised the blood-pressure and restored adequat circulation Other evidence of increased capillar permeability in the attacks was afforded by seria estimates of plasma-volume, and by the disappearanc curves of Evans-blue and radioactive iodinated serum albumin The full panorama of essentially negativ evidence as to the cause of the abnormal permeabilit must be sought in the original paper There was indeed some evidence of a vasodilator substance in serum there was a small amount of an abnormal macro globulin, and there was an increased amount of heparin precipitable protein But the search for an allergen wa unrewarded, and there was no response to steroid or anti-histamines The possibility that endometria products were gaining access to the circulation an affecting the capillaries was excluded by the failure o hysterectomy to control the attacks, and the subsequent oophorectomy similarly excluded absolute dependenc of the attacks on ovarian function Apparently th effect of vasopressin on the attacks was not observed, and the urine was not tested for hydroxyindole-acetic acid;

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[3] Walker J B *Post Grad med J* 1959, 35, 302
[4] Conn, J W *Diabetes*, 1958, 7, 347
[5] Fajans, S S Conn, J W *Diabetes*, 1954, 3, 296
[6] Duncan L J P *Quart J exp Physiol* 1956, 41 453
[7] Goto, Y , Kato, J , Takanami, A , Ohneda, A *Lancet*, Aug 27, 1960, p 461
[8] Jackson W P U *Post Grad med J* 1959, 35, 287
[9] Newburgh, L H , Conn, J W *J Amer med Ass* 1939, 112, 7
[10] Ashworth, M A., Haust, R E *Canad med Ass J* 1956, 74, 975
[11] Platt, R *Lancet*, 1959 i, 159
[12] Gordon, R S *ibid* p 325
[13] Clarkson, B , Thompson, D , Horwith, M , Luckey, E H. *Amer J* 1960, 29, 193

otherwise everything conceivable seems to have been done, with the conclusion "The reason for the sudden marked alteration in capillary permeability is unknown, as is the reason for its consistent occurrence during the premenstrual phase of her menstrual cycle."

The relation between the menstrual cycle and systemic disease has been reviewed by ROGERS[14]; the weight-gain in the premenstrual phase is due to salt and water retention rather than to any change in capillary permeability In this patient fluid retention may have determined the timing of the attacks, but cannot have been their primary cause. Less spectacular episodes of cyclical œdema are known to be far commoner in women than in men, and usually disappear after the menopause[15] Psychological factors have been shown to influence fluid balance in healthy people,[16] and even in patients with congestive heart-failure[17], and their importance is well recognised in premenstrual cyclic œdema.[15] Such factors cannot be easily dismissed in a patient with successive near-fatal crises, but it is one thing to recognise their importance, and quite another to say what they are or how they could act.

Although this sad story is not likely to be heard very often we have given it extensive notice, partly because the recorded observations may help in understanding any similar cases and partly because, despite its apparent uniqueness, this record may have some general application. An increase in capillary permeability has at times been postulated as a major factor in the œdema of cardiac failure or of acute nephritis Because of the complete dissimilarity between such states and the dramatic episodes in this patient (which were demonstrably due to increased capillary permeability) it seems unlikely that cardiac and nephritic œdema are largely due to abnormal capillary permeability—a view which accords with the low protein content of œdema fluid in patients with heart-failure or nephritis[18]

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[14] Rogers, J *New Engl. J Med* 1958, 259, 676
[15] Thorn, G W *Amer J Med* 1957, 23, 507
[16] Schottstaedt, W W, Pinsky, R. H., Mackler, D, Wolf, S *ibid* 1958, 25, 248
[17] Barnes, R., Schottstaedt, W W *ibid.* 1960, 29, 217
[18] Warren, J V, Stead, E. A. *Amer J med. Sci.* 1944, 208, 618.

Annotations

STUDENT AND FAMILY

THE system whereby medical students see nothing of patients during the first two or three years of their course is neither eternal nor universal Our forefathers often started their studies by going as apprentice to a practitioner, while in France the student may be allowed into the wards as soon as he starts training On the best ways of learning to swim, in medicine as in everything else, there will always be argument, but opinion is now turning against those who believe in several years' instruction before the student gets a sight of the water One of the ways in which some medical schools try to maintain his initial interest, and direct it usefully, is by giving him personal charge of a family, with which he may remain in touch throughout the years of his medical course

As will be seen from his article on p 957, Professor Prasad puts his trust in such a scheme as a means of recalling students from the artificialities of hospital medicine to the reality of daily life In practice, however, the Indian innovators might avoid some obstacles by studying American schools where, with similar objectives, such schemes have been tried with many different variants At Western Reserve the family study starts very early in the student's career, when he is present at a birth and afterwards takes an interest in the baby's development.[1] From the child his interest spreads logically to the parents, and so to the other children, whom he visits at home, more or less frequently, during the next few years, and at best this may be an invaluable piece of experience, introducing him to many different medical and social problems and reminding him always that people are people. On the other hand, compared with the traditional doctor-patient relationship, the student-patient relationship is somewhat artificial, and can be awkward the student may either settle down as a friend of the family (a role by no means to be despised) or he may attempt too much with too little knowledge Professor Prasad regards the preclinical student as insufficiently mature for such studies On the other hand, in the comprehensive care and teaching programme under Professer Reader at Cornell University,[2] where they come later in the curriculum, some students (perhaps because they are already in their fourth year) are not happy unless their task is regularised on conventional lines, with non-medical problems docketed for separate attention by the social worker Though others throw themselves into all the family difficulties, some critics have held that "exposure to overly complicated familial difficulties of patients have turned out to be more detrimental than helpful for certain students at the fourth-year level, allowing them to learn little of the possibilities of comprehensive care, but only of the limitations"[3] Some American schools defer this kind of practical-social teaching until the later stages of the curriculum their home-care programmes allow the student to take charge of a family, with full support from the hospital, at a time when he is already all but a doctor In many American schools, of course, social experience is still obtained in the traditional way by sending the students to work with "preceptors" in private practice

Another scheme which Professor Prasad describes is the allocation of tuberculous families to fourth-year students, who make a study of the whole situation and write it up Such projects are becoming commoner as a valuable part of medical education, and the student's critical study of a family, culminating in a report on one of its aspects, is perhaps the high spot of the clerkship in environmental medicine and community health now given at the State University of New York. Just as Professor Prasad has found it wise to construct a schedule of study, so Prof Duncan Clark and his colleagues at the Downstate Medical Center in New York have used a specimen draft, so that students need not be inhibited by having to think out the way in which their report shall be written. But in New York, as in Lucknow, quite a proportion of students turn to this work with real enthusiasm and sit up half the night writing illustrated notes of their observations Their comments on the action to be taken show that, unlike the majority of doctors in practice, the students of a modern American school are "psychologically oriented"

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[1] Pemberton, J *Lancet*, 1953, ii, 469
[2] Merton, R. K. Reader, G C. Kendall, P L. The Student Physician. Harvard University Press, 1957
[3] Goss, M. E. W *ibid*, p 249

Another useful means of teaching these senior students is a discussion of what was done for the patient, with an invitation to them to discover what was *not* done

PROGNOSIS IN MITRAL STENOSIS

THE sustained efficacy of mitral valvotomy is recognised,[1-3] but the long-term results should be compared with those of medical treatment only An excellent retrospective study from the era before valvotomy has been made by Rowe et al ,[4] who followed 250 patients (194 women and 96 men) with mitral stenosis until death or for at least ten years, 115 of the patients were followed for twenty years The cases were divided into four grades of severity at the time of the initial examination grade 1, no symptoms and normal rhythm, grade 2, mild symptoms with or without atrial fibrillation, grade 3, moderately severe symptoms with or without a major complication, grade 4, chronic heart-failure

During the first ten years the mortality was highest in the first five-year period, except in the symptom-free group Of the entire series 61% lived for ten years (84% in grade 1, 42% in grade 2, 15% in grade 3, and none in grade 4) At the end of ten years 40% of the whole series had remained unchanged, 20% had progressed to greater severity, and 40% had died The cause of death was known in 110 patients, 67 of whom succumbed to progressive heart-failure, 21 to arterial embolism (usually cerebral), 10 to pulmonary embolism, and 5 to subacute bacterial endocarditis before the introduction of antibiotics Of the 21 who died from arterial embolism 19 were women

In the 250 patients during the first ten years the prevalence of dyspnœa, pulmonary œdema, congestive heart-failure, atrial fibrillation, arterial embolism, and pulmonary embolism all increased, but oddly enough the prevalence of hæmoptysis remained at 9% When the patients were first seen 20% had atrial fibrillation, and the proportion increased to 33% at the end of the ten years During the ten-year period 30 patients, nearly all with atrial fibrillation, had 48 episodes of systemic embolism Associated systemic hypertension was present in only 6%

Of the 115 patients whose fate was known after twenty years, 43% were originally classified as grade 1, 45% as grade 2, and 12% as grade 3, in contrast to the original 250 patients, with 52%, 37%, and 10% in these three grades respectively 45% were still alive in the eleventh year, 30% in the fifteenth year, and 21% at the end of twenty years 40% of patients in grade 1 survived the full twenty years, but only 8% in grades 2 and 3 Major symptoms and complications increased with time as in the ten-year group, but pulmonary œdema and congestive heart-failure were more frequent than in the ten-year group Arterial embolism occurred in 26% of the 115 patients, again almost exclusively in women

Rowe et al [4] compared these results with those in other series The results were very similar to those reported by Grant,[5] who described the course of mitral stenosis over a ten-year period in 238 men More recently, Olesen [6] reviewed 271 patients with dominant mitral stenosis The severity of the disease and ages of the patients were greater than in Rowe's [4] group, and this was reflected in a ten-year survival of only 35%, c pared with 61%

Comparison of the survival curves of the three med series with the surgical series of Ellis et al ,[7] followed seven years after valvotomy, reveals appreciable dif ences 90% of the surgically treated patients were a at the end of seven years, compared with only 60% of composite medical series of 759 patients, and 45% Rowe's [4] series of 250 patients The superiority of surg over medical treatment for critical mitral stenosis is bo out by Donzelot et al [8] 157 patients with mitral sten treated medically were followed for from twenty mon to five years, during which time 71 died and 45 ot became worse none improved By contrast, of patients who were operated on, 133 improved, 14 did change, 2 became worse, and 16 died Admittedly, as of the patients treated medically were considered uns able for valvotomy owing to associated lesions or i versible heart-failure, the comparison is not strictly f but of 19 other patients who were all advised to unde valvotomy but refused, 11 died within five years, deteriorated seriously, and only 4 did not become wo This experience agrees with that of Harken et al ,[9] w reported that 17 of 19 patients died within a year refusing valvotomy

Mitral valvotomy thus appreciably improves the lo term outlook of mitral stenosis, and the immediate g results are usually maintained The data of Rowe et suggest that without surgical aid a patient with signific mitral stenosis who has symptoms when first seen ha probability of death by the end of ten years, and a stro probability by the end of twenty years Even the pati who is symptom-free when first seen has a 25% chance deterioration and a 16% chance of death by the end of t years, and a 60% chance of death after twenty years T greatest hazards are congestive heart-failure and p monary or systemic embolism The great predominan of women over men with systemic embolism in this ser is unexplained

On this evidence the case for mitral valvotomy for patients with mitral stenosis might seem overwhelmin but the issue is not quite so clear-cut The results purely medical treatment with effective antibiotics a improved methods of treating heart-failure would n probably be considerably better than at the time of t retrospective studies reported here Moreover, ma variables, such as the state of the mitral valve, the degr of incompetence and calcification, and other valve lesion cannot be assessed in retrospect Age is also obvious an important factor, and Rowe et al [4] point out that t survival-time was shorter in older patients Furthermor mitral valvotomy is not entirely without risk of morbid or mortality Restenosis occurs within five years approximately 1% of patients per year, often necessitati a further operation [1 2 10 11], but improved methods valvotomy by the transventricular route may diminis the incidence [11 12] Two major hazards to life associat with the operation are systemic embolism due to d lodgement of loose clots from the left atrium, and torre tial mitral incompetence which occasionally ens despite careful attention to technique There is so

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[1] Likoff, W Uricchio J F *J Amer med Ass* 1958, 166, 737
[2] Baker C Hancock, W E *Brit Heart J* 1960, 22, 281
[3] Ellis, L B Harken, D E., Black, H *Circulation*, 1959 19, 803
[4] Rowe, J C Bland, E F, Sprague, H B, White, P D *Ann intern Med* 1960 52, 741
[5] Grant, R T *Heart*, 1933 16, 275
[6] Olesen, K H Mitral Stenosis a follow-up of 351 patients Copenhagen, 1955
[7] Ellis, L B Abelman, W H , Harken, D E *Circulation*, 1957, 15,
[8] Donzelot, E , Heim de Balsac, R , Samuel, P , Beyda, E *Brit H* 1957, 19, 555
[9] Harken D E , Ellis, L B , Dexter, D , Farrand, R E, D J F *Circulation*, 1952, 5, 349
[10] Belcher, J R *Brit Heart J* 1958 20, 76
[11] Wilcken D E L *Brit med J* 1960, i, 681
[12] Logan A., Turner, R *Lancet*, 1959, ii, 874

evidence[13,14] that administration of anticoagulants may diminish the risk of valvotomy in patients with atrial fibrillation, while correction of iatrogenic mitral incompetence by open operation is feasible, though often extremely difficult

The value of mitral valvotomy in relieving symptoms and prolonging life in patients with critical mitral stenosis causing symptoms or systemic emboli is unquestioned, and no patient who needs the operation should be denied it under these circumstances unless definite contraindications exist It is doubtful whether the patient without symptoms or systemic embolism should be subjected to the operation as a prophylactic measure, but Bannister[15] claims that the risk of embolism in cases of moderate stenosis with trivial symptoms is so high that immediate operation should, he suggests, be considered unless the patient is young and still in sinus rhythm Certainly such patients, and indeed all patients with mitral-valve disease, should be kept under regular medical supervision so that appropriate action may be taken if deterioration sets in.

ASSESSMENT OF HEPATIC SIZE, SHAPE, AND CONTENT

ALTHOUGH the liver is the largest organ in the body, its sheltered position may cause difficulty in assessing its size and shape and deciding whether it is diseased Clinical examination is the most rewarding and least troublesome method to the examiner conversant with its surface markings[16] The lower edge is usually palpable in the healthy, and it is felt particularly readily in the emphysematous patient with a low-lying diaphragm Percussion, which distinguishes its upper border from the lung and the lower border from resonant viscera, is invaluable in detecting a small liver Occasionally confusion arises in distinguishing a low-lying normal liver from an enlarged diseased liver Factors contributing to a false impression of hepatomegaly include the subject's occupation and somatotype The well-developed diaphragmatic movements of a singer or athlete may be responsible for a low-lying, easily palpable liver In a correlation of the size and slanting angle of the liver with body-type, Fleischner and Sayegh[17] have drawn attention to the easily palpable low-lying normal liver of the ectomorph and the more horizontal high-slung liver of the mesomorph Antero-posterior and lateral radiographs may help to determine the "slant" of the liver, and screening will convey an accurate impression of the influence of the diaphragm on the position of the liver In special circumstances, induction of a pneumoperitoneum or gaseous gastric distension may help to distinguish the liver from surrounding structures

The use of radioactive isotopes to assess liver size, and particularly for the demonstration of filling defects due to hepatic metastases, is still at an experimental stage Rose-bengal, a dye which was commonly used to assess liver-cell function before bromsulphalein was introduced, s labelled with radioactive iodine, and its distribution in he liver is picked up by an external scintillation counter nd recorded on X-ray film[18,19] Radioactive rose-bengal is rapidly concentrated by liver cells but not by metastases, so space-occupying lesions of the liver can be mapped out as barren non-radioactive areas Unfortunately, a metastasis must be of considerable size before its presence is obvious by this technique, for, if small, it may be concealed by overlapping normal liver tissue.

Helander et al[20] in Sweden have attempted to increase the yield of information by using a somewhat similar isotopic technique in conjunction with hepatic venography Intravenous radioactive gold, which is rapidly taken up by the reticuloendothelial system of the liver, is detected by an automatic scanning scintillation counter, the liver "scintillogram" is altered by the presence of tumour tissue which cannot concentrate the gold Contrast medium, introduced by hepatic-vein catheterisation, discloses deformities of the hepatic vein and filling defects in the parenchyma of the segment of liver under examination Helander et al consider that with further development the scintillographic method will be the simpler and more useful for routine scanning of the whole liver The radiological technique is preferable for mapping a doubtful area, for it detects small multiple metastases when they are situated close to the veins filled with contrast medium

Percutaneous[21–23] splenoportography has also been used to detect hepatic metastases Primary or secondary neoplasm of the liver may produce sufficient distortion of the portal vein and its branches to be seen in a venogram, but similar appearances due to a large regeneration nodule in a cirrhotic liver may be confusing

These additional techniques for localising anatomical and pathological changes in the liver are still crude and imperfect With refinement, they may prove of the utmost help in the treatment of hepatic metastases by partial hepatectomy

MEASLES AND EPILEPSY

THE infectious fevers of childhood are liable to give rise to clinically obvious encephalitis, which may result in death or permanent disability in some places, indeed, the morbidity and mortality from measles encephalitis has been about the same as that from poliomyelitis Observations by Gibbs et al[24] now suggest that encephalitis due to the infectious diseases of childhood is much commoner than clinical observation suggests Electroencephalograms (E E G) were obtained from 1298 children admitted to hospital with measles, mumps, chickenpox, rubella, or scarlet fever Of 717 patients with measles 381 (53%) had abnormal E E G s during or immediately after the acute phase of the disease, and of these only 37 had clinical evidence of encephalitis The E E G changes, which were unrelated to changes in body-temperature, are ascribed [illegible] Gibbs et al to encephalitis In the great majority [illegible] patients these abnormalities subsided, but in [illegible] they persisted for months or years The fol[illegible] is not yet complete, but already 2 patient[illegible] with increasing E E G abnormality [illegible] vulsions, and in 1 of these the [illegible] "idiopathic epilepsy" Of [illegible] abnormal E E G which [illegible] have shown behaviour [illegible]

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[3] Storm, O, Hansen, A. T *Circulation*, 1955, 12, 981

[4] Goodwin, J F *in* Pathogenesis and Treatment of Occlusive Arterial Disease (edited by L. MacDonald) London, 1960

[5] Bannister, R. G *Lancet*, Aug 13, 1960, p 329

[6] Sherlock, S Diseases of the Liver and Biliary System, p 5 Oxford, 1958.

[7] Fleischner F G Sayegh, V *New Engl J Med* 1958, 259, 271

[8] Freidell H L, MacIntyre, W J, Rejali, A M *Amer J Roentgenol* 1957 77, 455

[9] Fee, D A., Fedoruk, S O *New Engl J Med* 1960, 262, 123

[20] Helander, C G, Jo[illegible] *Acta radiol*, Stockh [illegible]

[21] Leger, L [illegible]

[22] Figley, M M [illegible] *enterology*, [illegible]

[23] Turner, [illegible]

[24] Gibbs, [illegible] L, Carr[illegible] [illegible]

Transport

It has been shown that the transportation of these infants over considerable distances does little harm (Forshall and Rickham 1953) provided an experienced nurse accompanies the infant The baby is usually transported lying flat on his side in a carry-cot, warmth is supplied by hot-water bottles In all cases of intestinal obstruction or suspected obstruction a no 3–4 soft rubber catheter is passed through a nostril into the stomach, the nurse aspirates the stomach every ten minutes Should the infant none the less aspirate mucus or vomitus, the nurse sucks out the pharynx by means of a mucous extractor (Rickham 1957a) An oxygen cylinder and an apparatus for humidifying oxygen are at hand in the ambulance The greatest care should be taken to prevent the body-temperature falling during transport, especially in premature infants

Admission

Babies from maternity departments are admitted directly to the main ward of the unit Infants born at home or admitted via a general pædiatric unit, and any baby in whom there is the slightest suspicion of contact with infection, are nursed in isolation cubicles for several days before being transferred to the main ward Despite great care, cross-infection occasionally occurs—nearly always a specific *Escherichia coli* infection

Preoperative Treatment

On admission, infants needing operation are placed in special surgical incubators at a temperature of 85°F, in an atmosphere of 100% humidity Minor surgical, radiological, and anæsthetic procedures as well as balance tests can be carried out in the incubators without much disturbance of the children (Rickham and Jenkins 1960) The body-temperature is recorded by an electric thermometer, frequent readings can be made without moving the infants Investigation and, as far as possible, treatment of babies with subnormal temperature are deferred until the body-temperature has risen to normal Preoperatively penicillin, streptomycin, and vitamin K (1 mg) are injected transmuscularly In the cases in which investigation of the blood chemistry is essential, 0 1 ml of blood is obtained by heel stab (Rickham 1957b) All infants have a cut-down infusion before operation, only a minority require correction of dehydration and electrolyte imbalance preoperatively

In cases of intestinal obstruction, constant gastric suction at a negative pressure of 20 cm of water via a catheter passed through the nose is instituted Continuous gastric suction, will often completely deflate a distended abdomen in a newborn infant, as well as preventing aspiration of vomitus

Postoperative Treatment

The infants are transported back from the theatre to the unit in their incubators, and they are nursed in incubators during the immediate postoperative period Many of these neonates, and especially those operated on for obstruction of the alimentary tract, need protracted low-pressure gastric suction and intravenous therapy, under accurate biochemical control (Rickham 1957c) Conscientious, skilled nursing and continuous supervision by the surgeon are essential in the immediate postoperative period The commonest cause of sudden death during this period is inhalation of vomitus or mucus, a trolley carrying all the necessary equipment to deal with this emergency is always ready in the ward

Operation and Anæsthesia

The importance of correct replacement of blood-loss (Rickham 1954a, 1959c) cannot be overemphasised The great advances in neonatal anæsthesia, the routine use of endotracheal anæsthesia with controlled respiration, using oxygen, nitrous oxide, and suxamethonium chloride (Rees 1958) have made protracted operations on neonates relatively safe As no ether or cyclopropane is used, diathermy can be employed, and this considerably reduces blood-loss and operation-time

Prematurity

The cases admitted to the unit differ from cases in previously published series, in that practically every infant with a surgical abnormality born in the area of drainage is included This explains the high incidence of very premature infants and of infants with multiple, severe, malformations We have only very occasionally saved an infant who, in addition to a malformation amenable to surgery, has a malformation of one or several other systems (e g, cardiac or cerebral) It seems likely that in these children the prognosis will always be poor It should, however, at least theoretically, be possible to save more premature infants with a single abnormality Our operative mortality in premature infants is still very high 222 (35%) of the 663 infants operated on in the past six years were premature (under 5½ lb in weight) While the operative mortality of the 441 full-term infants was 12 4%, that of the 222 premature infants was 50 4%, and in the 87 infants weighing under 4½ lb, the operative mortality rose to 60 9%

This high mortality in premature babies is partly due to the high incidence of multiple abnormalities in these infants—in our series 32 9%, as opposed to 10 9% in full-term infants There is great difficulty in nursing these infants through the postoperative period (Rickham 1957d) The swallowing and coughing reflexes are incompletely developed, and aspiration of mucus and vomitus is common The immature state of the lungs predisposes to pulmonary complications, and the incidence of sclerema is higher in premature infants Satisfactory results have occasionally been achieved, our smallest surviving infant with œsophageal atresia weighed 2 lb 8 oz, with pyloric stenosis 2 lb, and with ileal atresia 3 lb

Conditions Treated

The surgical conditions treated in the unit have been grouped under fifteen headings (see accompanying table) † The cases are further subdivided into four categories (1) full-term infants with a single major malformation, (2) full-term infants with multiple malformations, each of which occurring alone would endanger life, (3) premature infants with one major malformation, (4) premature infants with multiple malformations The table shows that the operative mortality for full-term infants with one major malformation is relatively low The operative mortality in any series will depend on the distribution of infants between the four groups

Malformations of Central Nervous System

The most common type of case admitted is severe spina bifida with or without hydrocephalus Formerly these cases seldom came to surgery before they were 4 weeks of age (Rickham 1957e) Recent advances in the treatment of myelomeningocele, and especially the introduction of the Spitz-Holter valve for the drainage of hydrocephalus (Spitz 1959), have resulted in the

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† To avoid confusion cases with multiple malformations are shown only once—i e, under the main malformation

NUMBERS OF CASES IN MAIN GROUPS OF DISORDERS OPERATED ON IN THE NEONATAL SURGICAL UNIT BETWEEN MAY, 1953, AND MAY, 1959

Condition	Total no	Total deaths	Full-term infants with one malformation*	Full-term infants with multiple malformations*	Premature infants with one malformation*	Premature infants with multiple malformations*
Malformations of central nervous system	85	*13*	72 (*10*)	3 (*0*)	9 (*2*)	1 (*1*)
Malformations of upper respiratory tract	14	*2*	10 (*0*)	1 (*1*)	3 (*1*)	0
Œsophageal atresia	83	*43*	26 (*4*)	11 (*6*)	20 (*9*)	26 (*24*)
Pyloric stenosis (premature infants only)	37	*4*			33 (*1*)	4 (*3*)
Intrinsic intestinal obstruction	57	*13*	26 (*1*)	7 (*1*)	14 (*3*)	10 (*8*)
Extrinsic intestinal obstruction	55	*2*	36 (*0*)	1 (*0*)	13 (*0*)	5 (*2*)
Peritonitis	41	*15*	25 (*4*)	1 (*1*)	14 (*9*)	1 (*1*)
Meconium ileus	23	*19*	9 (*6*)	2 (*2*)	9 (*8*)	3 (*3*)
Hirschsprung's disease	28	*5*	23 (*4*)	0	5 (*1*)	0
Anal and rectal atresia	65	*12*	35 (*0*)	12 (*5*)	11 (*2*)	7 (*5*)
Exomphalos	57	*23*	31 (*5*)	8 (*4*)	11 (*9*)	7 (*5*)
Malformations of genitourinary system	38	*9*	27 (*3*)	3 (*2*)	5 (*1*)	3 (*3*)
Diaphragmatic hernia	18	*7*	10 (*1*)	0	7 (*5*)	1 (*1*)
Obstructive jaundice	8	*1*	7 (*0*)	0	1 (*1*)	0
Tumours	20	*3*	17 (*2*)	0	3 (*1*)	0

* No. of deaths in italics.
In cases with multiple malformations the case is shown only once—i.e., under the main malformation.

admission of more and more newborn infants. Myelomeningoceles and myeloceles are now operated upon as soon as possible after birth, before the covering membranes become infected. In more than half of the cases, hydrocephalus rapidly develops postoperatively. Insertion of the Spitz-Holter valve in patients of this age is associated with some special difficulties, but on the whole the results have been encouraging. There is little doubt that there will be a further increase in the number of cases with these malformations admitted to the unit.

Obstruction of Upper Respiratory Tract

Apart from rare instances of laryngeal or subglottic stenosis necessitating urgent tracheotomy, such cases are of two main types. The first is severe micrognathia, usually associated with cleft palate (Pierre Robin syndrome), in which there may be severe respiratory difficulty in addition to difficulty in feeding. Skilled nursing with the infant in the semiprone position and feeding by gavage will usually overcome these difficulties, but occasionally tracheotomy is required and in 1 case gastrostomy had to be performed. The second type is bilateral posterior choanal atresia, treatment of which consists in perforating the bony or cartilagenous septa occluding the posterior nares, thus establishing a nasal airway. In both types of case, postoperative treatment is lengthy and difficult and taxes the nursing staff to the utmost.

Œsophageal Atresia

It will be noticed from the table that the operative mortality in full-term infants with œsophageal atresia, without other malformations, is small. Unfortunately the number of premature infants, and especially the number of premature infants with multiple malformations, in this series is very high (Forshall 1957a), and the mortality in these groups is enormous. The commonest associated malformations are severe cardiac lesions, incompatible with survival for more than a few days, and rectal and duodenal atresia. Duodenal atresia carries a very bad prognosis. Today leaks in œsophageal anastomoses are not necessarily fatal, but necessitate prolonged and often difficult postoperative management. Nursing these children in incubators in an atmosphere of 100% humidity, restriction of intravenous fluids, and avoidance of unnecessary handling are the main factors which help to lower the mortality.

Pyloric Stenosis

Most infants with pyloric stenosis are admitted to, and treated in, the general pædiatric surgical wards, only premature infants are admitted to the unit. Of the 33 cases, nearly a third weighed less than 3½ lb. Of the 4 deaths 1 was due to intracranial birth trauma. 2 infants had a blood dyscrasia of prematurity, both weighed less than 3 lb., and, in both, severe bleeding into the lungs and intestinal and urinary tracts started shortly after operation.

Intrinsic Intestinal Obstruction

In roughly half the cases, the obstruction was in the duodenum (Forshall 1947), and in the other half it was in the jejunum or ileum, in only 2 cases was the obstruction in the colon. Most of the cases in this group had atresia, in roughly a quarter of the cases there was a high-grade stenosis. About a third of the duodenal obstructions were associated with annular pancreas (Rickham 1954b). In full-term infants without other gross malformations survival-rate was high.

Extrinsic Intestinal Obstruction

These were mostly cases of anomalous rotation of the midgut with volvulus or of obstruction due to intraperitoneal bands, a few had strangulated herniæ. In only 1 of these cases was it necessary to open the intestinal lumen, which explains the low operative mortality. 1 death occurred in a premature infant and was due to kernicterus.

Peritonitis

Under this heading, two different conditions are included: sterile meconium peritonitis due to intrauterine extrusion of meconium from the bowel into the peritoneal cavity (Forshall et al. 1952), and bacterial peritonitis (Rickham 1955, 1959d). Many of the infants had intestinal atresia, perforation, or gangrenous gut. The mortality was high.

Meconium Ileus

This is still the most fatal condition encountered in neonatal surgery. Most children now survive the operation to relieve intestinal obstruction, but die of fulminating bronchopneumonia in the first few postoperative days or weeks. Of 23 cases only 10 left the unit alive, and all but 4 died in the first year of life.

Hirschsprung's Disease

Practically all cases of Hirschsprung's disease are now seen as neonates presenting with symptoms of intestinal obstruction. In most cases the obstruction can be relieved by enemas or by passing a flatus tube, only to recur after a few days or weeks. Several of our earlier cases died of fulminating staphylococcal enteritis or aspiration of vomitus. Since a colostomy has been instituted as soon as the diagnosis is made, the mortality has fallen. Rectosigmoidectomy is performed when the infant is over 15 lb. in weight.

Anal and Rectal Atresia

The operations for anal abnormalities are relatively minor, and there is a very low operative mortality. An abdominoperineal pull-through operation is used for rectal atresia, this is a severe operation, but the mortality is not excessive. Most deaths in this group occurred in babies with associated malformations. Œsophageal atresia and malformations of the cardiovascular and urogenital system are especially common, cardiac lesions are not infrequently of such severity as to be at present incompatible with life (Forshall 1957b).

Exomphalos

The results in this group are strikingly poor. Exomphalos minor is not associated with any operative mortality. Exomphalos major not only is a dangerous condition per se, but is commonly associated with other serious malformations Further, many of the cases in this series were grossly premature This explains the fact that, while only 1 in 8 full-term infants with exomphalos died, the total mortality was nearly 50%

Malformations of Genitourinary System

This group includes a wide variety of lesions—mainly obstructions of the urinary tract causing renal failure shortly after birth Most of the infants survived operation, but in many renal damage was so severe that the long-term prognosis is poor

The number of cases of gross malformations of the urinary tract operated on in the unit is increasing each year The operative treatment of ectopia vesicæ (closure of the ectopic bladder and splayed-out pelvic ring) in the immediate postnatal period will augment the number of cases admitted in the future

Diaphragmatic Hernia

The number of infants with this malformation is relatively small The mortality is again high because of the high incidence of associated deformities incompatible with life—especially cardiac and pulmonary malformations

Obstructive Jaundice

Only a few of the children with obstructive jaundice will come to surgery during the neonatal period Usually these infants are more than 4 weeks old before gradually increasing jaundice results in their reference to a pædiatric surgeon This explains the relatively small number admitted to the unit Exploration, liver biopsy, and, if possible, an operative cholecystogram should be carried out in cases in which a mechanical obstruction cannot be excluded by laboratory tests In only about 10% of these cases will a mechanical block of the extrahepatic bile passages be found and operative correction become a possibility (Hall 1957)

Tumours

Sacrococcygeal teratoma is the commonest of tumours in newborn infants Most of these tumours are benign, but occasionally malignant tissue is found in a teratoma removed immediately after birth Early excision is, therefore imperative A wide variety of benign and malignant tumours was encountered, individually rare, the total is not inconsiderable

Follow-up of cases

All infants discharged from the unit are followed up as outpatients Monthly outpatient clinics are held in certain centres outside Liverpool to save the mothers travelling too great distances In the city of Liverpool the care of premature infants, after discharge, is greatly aided by the premature domiciliary nursing service provided by the medical officer of health

Developments

The unit was started with the absolute minimum of financial aid Equipment was very limited, and, because of the rapidly increasing numbers of admissions, space soon became inadequate In addition, there were inadequate arrangements for nursing the many premature infants admitted, and the accommodation for nursing mothers was unsatisfactory

The experience gained in six years has enabled us to formulate various improvements, and, with the generous help of the regional board and the hospital management committee, the unit has now been reorganised The main improvements are the provision of 2 more isolation cots, the building of an air-conditioned " hot room " with a constant temperature of 85°F, and a humidity of 90%, large enough to hold 6 incubators for premature infants, and the addition of a small ward for convalescent infants, holding 1 cots Infants nursed in the hot room can be taken out of the incubators without lowering their environmental temperature and humidity, thus facilitating nursing and minor operative procedures There are now 12 cots, 6 incubators, and rooms for 2 nursing mothers in the reorganised unit In addition, there have been a number of structural improvements, the most important being a sister's room with glass walls allowing simultaneous supervision of the two wards and the " hot room "

Conclusions

There is little doubt that the Liverpool unit for the surgical treatment of newborn infants has proved its value It is of course possible to achieve good results nursing such infants in general wards or side-wards, but the work is much facilitated by concentrating cases in one unit Even more important, the unit provides ideal conditions for the training of medical and nursing staff, and adequate material for postgraduate teaching

The Liverpool region lent itself to this experiment because the area is small but thickly populated The inclusion of North Wales has shown that distance is no bar to the establishment of an efficient neonatal surgical service Such a centre is best situated within a large children's hospital attached to a university, thus insuring the cooperation of pædiatricians, pædiatric anæsthetists, pathologists, biochemists, radiologists, and the various research-workers necessary for the development of this still young branch of surgery Most of the provincial university centres in the country have the requisite staff and conditions for the establishment of such a unit

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THE INDUSTRIAL THERAPY ORGANISATION (BRISTOL)

A DEVELOPMENT OF WORK IN HOSPITAL

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INDUSTRIAL work in hospital has been reviewed by Charlton (1959), who found that 58 hospitals in this country were carrying out industrial therapy

At Fishponds Hospital, which has altogether about 1200 patients, the capacity of our scattered factory rooms was increased from 14 patients in January, 1958, to 385 patients in December, 1959 The work is mainly manufacture of ball-point pens, box-making, stamp preparation, and telephone dismantling The department functions under joint nursing and industrial supervision, at present there are 6 industrial and 8 nursing staff (3 unqualified women, 3 unqualified men, and 2 qualified men)

The patients work 25 hours a week, singly or in teams or groups, and are paid " the rate for the job " Total earnings by patients in November, 1959, amounted to more than £1300 The hospital management committee deduct 10%, but, as Stanley (1959) points out, this does not benefit the hospital nor the patients who earn the money This disagreeable anomaly should be rectified

To occupy consistently a third of the patients in a chronic hospital is obviously a desirable aim, but it is not an end in itself Patients tend to settle down as they have been encouraged to in the past, with a slightly better standard of living, and an "industrial aristocracy" tends to replace the old privileged maintenance-department worker The ultimate aim of discharge may be lost sight of by patients and by staff

The standard of work maintained by patients in the hospital industrial therapy department has been consistently high, and the industrialists have been impressed by the quality of their work. It was difficult initially to overcome the inertia which beset the people whom we wished to interest, but with the help of a director of one of our firms, a considerable number of industrialists were persuaded to visit the hospital and see the patients at work They were impressed by the commercial possibilities and by the philanthropic aspect of the work, and felt that further employment-training is necessary if patients are to be re-employed in open industry With this aim in view Industrial Therapy Organisation (Bristol) Limited was formed

I T O (Bristol) Ltd, is a non-profit-making company limited by guarantee and having registered offices in York Street, St Phillips Marsh, Bristol It has been formed to administer a scheme designed to offer medically and industrially supervised employment training under conditions approximating as nearly as possible to ordinary factory conditions, as a second stage toward complete industrial rehabilitation In the third stage of rehabilitation, worker-patients who improve under these conditions will be taken by sympathetic employers for a further period of training under "open" factory conditions and will subsequently, if successful, be employed if possible or be recommended by the employer

The chairman of the company is chairman of the Engineering and Allied Employers' West of England Association.

The Churches are represented by the Bishop of Bristol, the Bishop of Clifton, the president of the Bristol Free Church Federal Council, and the industrial adviser to the Bishop of Bristol Civic interests are represented by the Lord Mayor of Bristol, two justices of the peace (one of whom is the chairman of the Fishponds H M C), the chairman of the health committee and the chairman of the mental-health subcommittee of the local authority, and the medical officer of health The chairman of the South-Western Regional Hospital Board has agreed to serve together with an industrial medical officer, a consultant psychiatrist, and a general practitioner Industry is represented by the directors of 9 leading firms in the city, the chairman of I T O and his deputy, the regional controller of the Ministry of Labour, and the regional industrial adviser of the B B C The regional secretary and the local secretary of the Transport and General Workers Union and the president of the Bristol Trades Council, and our public-relations officer also serve on the board Local firms of solicitors and of accountants supply us with their advice

There was an initial storm in a teacup before the formation of I T O was proposed An ill-informed statement at the Bristol Trades Council gave rise to such headlines in the local press as "Mentally Ill in Danger" (*Western Daily Press*, Oct 10, 1959), and the word "exploitation" was used in reference to the work of patients in hospitals When, however, trade-union representatives visited the department and inquired into its aims and operation, the Bristol Trades Council were assured by their president that there was no exploitation and that the work was of practical therapeutic benefit (*Bristol Evening Post*, Jan 22, 1960) Thereafter, the unions have not opposed industrial therapy in hospital nor the formation of I.T O, but have been strong in support—in the case of the Transport and General Workers Union, strong in financial support Mr Frank Cousins, general secretary of the Transport and General Workers Union, when he visited the factory, described I T O as "a wonderful experiment" and as a "worth-while project" and added "We are proud that we have been able to do something to help I T O" (*Western Daily Press* March 26, 1960).

Premises

I T O has leased a disused school in York Street, St Phillips Marsh

This building was in very poor repair but was renovated by one of the participating firms It contains about 7250 sq ft of floor space Daylight lighting is good, but all electric wiring and fitments have had to be renewed. Heating is by means of a rather antiquated coal-burning furnace with hot-water circulation, in the summer this will be converted to oil Sanitary facilities are adequate, but much work had to be done on the water and drainage systems The roof also needed much attention, most of the lead having been removed Apart from factory space, we have a fair-sized canteen reasonably furnished, a general administrative office, a rest-room, and a medical office.

Finances

It is not proposed to establish I T O as a Remploy-type factory nor as a sheltered workshop, but rather as a training factory, stimulating initiative We hope that, as such, it will be self-supporting The money necessary to start has been contributed by various people—mainly by industry, with substantial sums from the Bishop of Clifton and from the Transport and General Workers Union The industrialists placing work with I T O pay the full labour costs of the job and have agreed to add $33^1/_3\%$ on cost to this price, this will cover the factory overheads The success of the worker-patients will thus be the only source of income of I T O

The main sources of expenses have been estimated as follows

Staff—Exclusive of medical and nursing supervision, it is estimated that 150–200 operatives would require a full-time staff of 8 a secretary (salary £750), a works manager (salary £1000), general supervision, approximately 5 (£2500), general labourer (£500), total £4750

Other expenses—Rent, £450 per annum, heat, light, and repairs, £1500, telephone, £100, general supplies, cleaning material, &c, and stationery, approximately £500

It was thus envisaged that the Organisation could be run for a total outlay of £7500 per annum

With an on-cost charge of $33^1/_3\%$ on work invoiced, it is estimated that the Organisation would require a turnover of approximately £28,000 per annum to be self-supporting If the average pay were £5 a week, 120 operatives would be required to achieve this turnover, and this is probably attainable

Medical and Nursing Supervision

The hospital management committee of the Fishponds Hospital agreed to allow nursing supervision for hospital patients, and we have started with a nursing supervisor, a ward sister, a charge nurse, and 2 unqualified staff, 1 of whom is a student male nurse Medical supervision is provided by the doctors who are in charge of the patients, but it is hoped that in the future some more definite arrangement may be possible The medical officer of health has seconded a health visitor, who at present is working half-time and whose prime duty will be to act as social worker As additional patients come from the community, more social workers will be seconded by the medical officer of health When other hospitals send patients they will be expected to provide nursing supervision for them We have arranged for a weekly staff meeting of nursing, social, industrial, and medical workers

Choice of Patients

To start the I T O factory on March 7, 1960, 20 patients were chosen from among those who had a good record in the industrial therapy department of Fishponds Hospital They were chosen by consultation with doctors and nurses, nursing supervisors, and industrial supervisors Regard was paid to industrial ability, stability, and sociability These 20 patients were joined at work by 5 who had been attending Fishponds Hospital as day patients from their own homes We began with the assembly of ball-point pens for Messrs Tallon Ltd Subsequently some box-making and stapling and gluing machinery were installed by Messrs E S & A Robinson, and a further 30 patients started from the hospital At present 61 patients (21 male and 40 female) attend daily from Fishponds Hospital and 18 day patients (12 male and 6 female) from their own homes

We anticipate that the complement of the factory at full capacity will be 120–150 After the " teething troubles " have been overcome, the factory will offer facilities to other patients in the Bristol clinical area according to the following procedure

I T O will accept applications for places in the factory from all consultant psychiatrists in the Bristol clinical area and from doctors in charge of day hospitals and occupational therapy departments, and from the medical officer of health No applications will be accepted from patients directly In the event of more than one application for a vacancy, the selection will be made by the medical directors of I T O Applicants will be accepted for a month's initial practical trial, following which the industrial, nursing, and medical staff will review each patient's suitability for further training During this assessment period earnings will be limited to £2, to obviate difficulties with National Insurance If the patient proves suitable, training will be continued, if unsuitable, the decision will be discussed with the doctor who referred the patient No subnormal patients will be accepted until the needs of chronic psychotics have been assessed

Since I T O is not a remploy factory nor a sheltered workshop, there must be movement of patients through the factory if it is to fulfil its purpose Its capacity is unlikely to exceed 150 places, so the time that any patient may remain must be curtailed No limit has been stated, but, when it is apparent on the basis of psychiatric, industrial, and nursing reports that the patient is no longer making progress and is unlikely to proceed further in industrial training, he must then be discharged from I T O Possibly at this stage patients will be acceptable in Remploy factories or in sheltered workshops The Ministry of Health is certainly more aware of the needs of the chronic psychiatric invalid than in the past, and it has emphasised the need to prevent chronicity in mental-hospital patients (Ministry of Health 1959) I T O is now considering the possibility of providing work for patients on a more permanent basis

Terms of Employment

Hours of Work

The patients work from 8 15 A M to 5 15 P M five days a week with one hour's lunch-break and two quarter hour tea-breaks As part of the training routine patients " clock in " and " clock out " as in an ordinary factory

Transport

22 patients travel by hospital bus for which no charge is made, and 36 by a bus chartered by I T O at preferential rates As the patients ride in each bus alternately, the overall cost per patient will be 3*s* 4*d* per week Outpatients make their own travel arrangements

Food

To provide in the factory a canteen which could supply a cooked meal at midday has been impossible owing to the initial outlay and the consequent high cost to the patient of meals Patients therefore bring a packed lunch, and hospital patients have a cooked meal when they return in the evening

Patients' Finances

I T O does not aim to pay big wages, but rather to provide further training under factory conditions The amount earned will largely depend on the type of work available in the factory Wages must be greater for a forty-hour-week than they have been for a twenty-five-hour week in hospital, otherwise the main incentive will be lost

There are three main administrative departments whose regulations act as a financial deterrent to patients in the initial stages of industrial rehabilitation—the Ministry of Health, the Ministry of Pensions and National Insurance, and the National Assistance Board

The *Ministry of Health's* (1958) memorandum on the recovery of part costs from patients going out to remunerative work was designed to cover circumstances very different from those created by I T O —namely, those of a patient who goes out to work full-time from hospital and who earns normal full-time wages of £6–£10 per week In the case of patients earning £2–£5 a week the terms of the memorandum stifle initiative, for example, working full-time at I T O, a single man with no dependants and no sickness allowance must earn £4 a week gross to have £1 13*s* 4*d* net In hospital, working a twenty-five-hour week, he can earn up to £2 a week without complication, so by doubling his effort and working an additional fifteen hours a week he will sustain a loss of 6*s* 8*d* To mitigate this position the Ministry has agreed that " the formula in H M (58) 72 may be modified by allocating £2 15*s* to the patient, instead of £1"

The regulations of the *Ministry of Pensions and National Insurance* are an even greater danger, especially for the patient whose wife and family are in benefit. Earning over £2 a week entails the cessation of National Insurance benefits for a wife and children, and the patient becomes liable to National Insurance contributions Since the earnings in I T O are unlikely to exceed £4–£5 per week (less in the initial stages), a class-2 (self-employed) National Insurance contribution represents a very high proportion of earnings, the disproportion is greater the lower the earning group, the contribution being 30% of £2 or 15% of £4 per week Not surprisingly, therefore, patients " hold back " and are virtually prohibited by regulations from exercising their initiative, which might lead to discharge and to their ceasing to be a charge on State funds

National Assistance Board—The Ministry of Health informed us that the N A.B would be able to meet the essential needs of the patients' dependants when the National Insurance allowance ceases, and that the N A B would in many cases compensate for the loss of dependants' part of sickness benefit. Local officials of the Ministry of Pensions and National Insurance and of the N A B have been most helpful, but lack of resilience in their regulations render individual cases of hardship inevitable when patients exceed a low limit of earning

Furthermore, a patient who qualifies to pay a board-and-lodging charge to hospital and who has dependants drawing National Assistance may find that the Ministry of Health and the National Assistance Board are each claiming from his earnings—for board-and-lodging and for dependants' allowance respectively

The report of the National Insurance Advisory Committee on the Question of Long-term Hospital Patients (1960) declared that there must be a point where a patient's earnings become inconsistent with his receiving National Insurance benefit, and the committee concluded that there was no evidence at the present time that the earnings limit of 40*s* a week was acting as a disincentive In I T O we have no doubt that the £2 limit acts as an obstacle in the initial stages of work outside hospital when earnings are low and depend on the patient's efforts The committee considered that the limit "should remain at 40 shillings per week for the present" It obviously foresaw that changes would be necessary, and I consider that in the present circumstances further consideration is essential

Unlike short-term illness, long-stay patients are not unfit for work today and fit for full-time employment tomorrow It will require time to re-establish the habit of normal work, and in most cases failure will result We wish to teach patients to assume normal responsibilities—to pay their National Insurance contributions, to pay income-tax if due, to pay for all or part of their keep, their transport costs, and their meals at work—but this must await the third stage of rehabilitation when the patient draws a full economic wage If the Ministry of Health (1958) and the National Insurance Advisory Committee believe in the therapeutic value of work, as they say they do, then together with the N A B some scheme must be devised which will encourage patients to work

Social Resettlement

The Medical Research Council (1959), discussing the conditions of resettlement of schizophrenics, says

> "It appeared likely that a proportion of these patients could be restored to life in the community provided that their social behaviour was such as to permit of their being discharged from hospital and of free association with healthy people"

Brown et al (1958) pointed out that, apart from the clinical state of the patient on discharge and his success in securing employment, the finding of suitable accommodation was of paramount importance It is unreasonable to expect a patient who has spent many years in the artificial atmosphere of hospital to settle immediately in the community when he obtains employment As the industrial training of a patient may take a considerable time, so too may his social training Together with industrial training and resettlement must go social rehabilitation Clark and Cooper (1960) describe an experiment in Cambridge which they call a psychiatric halfway house

Their hostel was financed by S O S, a charitable organisation (with aid from the Cambridge Mental Welfare Association and the county council) They conclude that such a house is of value to a limited group of people and suggest that, for a catchment area of 360,000, 16 places would be adequate They chose only patients who were in work or capable of finding employment within a month and who were deemed capable of achieving independent social life (in lodgings at least) within six months Possibly these requirements are rather rigid, and if they were more flexible, there might be more patients suitable for admission, but it speaks well for the selection that 10 out of 19 schizophrenics were discharged in the first year

Especially in view of the Mental Health Act (1959), I consider that the social reorientation and re-education of patients should be undertaken jointly by the hospital and local authority In Bristol we have discussed possibilities with representatives of the housing and the health committee I would like to see developed on the hospital estate (but removed completely from the hospital—on the opposite side of a main road) a row of 6–8 standard council houses such as patients may expect to live in on discharge, these houses would be built by the local authority and be jointly administered by hospital and local authority With a minimum of supervision—e g, a male nurse and his wife in one of the houses—discharged patients still undergoing industrial rehabilitation would occupy these houses as tenants, paying rent and learning again how to live socially acceptable lives These proposals are still in the embryo stage, but the hospital management committee favour the scheme, as does the chairman of the local authority's housing committee

If such a scheme of industrial and social rehabilitation were supported by the goodwill of the great national voluntary organisations, then at last there would be some real hope for the successful reintegration of the long-stay patient into the community

My thanks are due to those people whose goodwill and enthusiasm have made this experiment possible—particularly to Mr John P Turley, director of Messrs Tallon Ltd, and managing director of I T O (Bristol) Ltd, without whom the project would not have come into being

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Medical Education

FAMILY STUDIES BY STUDENTS

Innovations at Lucknow

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THE undergraduate student should see health and disease in their natural setting This helps him to learn to look beyond the individual patient, to the family in which that patient lives, to his work and play, and to his social and cultural background The student has to realise that the unit of his work is the family—not merely the sick person who first appears at the clinic

In India the undergraduate curriculum is overloaded with diagnostic and therapeutic medicine of the hospital type Few colleges give the student opportunities to work and observe in health centres, or with general practitioners or in families He remains so preoccupied with clinical and laboratory findings that he gives little thought to the human, psychological, biological, physical, and social factors operating in the family or in the community In medical education, therefore, provision has to be made for the study of man in disease in addition to the usual study of disease in man

One of the suggestions made at the 1959 W.H.O. conference on mental health was that students should follow one family through health and disease over a number of years.[1] Departments of social and preventive medicine can suitably take the initiative in such a family-study programme.

HOW AND WHEN

At Lucknow the teaching of social and preventive medicine is spread over the preclinical and clinical years. A rural health centre at Sarojini Nagar is being developed to give field training to undergraduates and preregistration graduates, and a family-study programme is being introduced for the undergraduates. At present we have a five-year course (after intermediate science examination in physics, chemistry, and biology has been passed) and during his third and fourth years the student acts as family adviser to two families—one family with a mother and a growing child and another family with a case of a chronic disease. The study will help the student (1) to get a better understanding of the relation of health and disease to the total life of the family, (2) to observe normal growth and development and any departure from it, and also the means for maintaining normal health, and (3) to appreciate the economic, social, and emotional situations created by disease and disability. The department has on its staff a medical social worker to help and guide the students in this programme.

Some recommend[2,3] that students in their preclinical years should be given families for study, but this is not generally favoured in India[4] and I think it inadvisable. The student's average age on entry in 1959–60 was 19.7 for men students and 18.3 years for women, and at this age they are not mature enough to create and maintain good rapport with the families. They would not be able to give the medical advice, or arrange the medical relief for which the families would ask, yet they might start playing the role of a doctor, which would be undesirable both for them and for the family.

In the preclinical years it is better to give some introductory lectures and then hold clinical conference demonstrations (as is now done in Lucknow once a month[5]) at which selected patients are presented with their families, in cooperation with other departments. Such a conference is essentially "preclinical"—i.e., it is concerned with the circumstances and condition of the patient more than with his disease. In the analysis with which the conference concludes the chain of causation is examined to show where this could have been broken. The aim is to lead students to think in terms of maintaining normal health, of the social causes operating in disease, and of the need for prevention, early detection, and early treatment.

A SUCCESSFUL PROJECT

In 1958 and 1959 the fourth-year students at Lucknow, who number about 160 per year, were each allotted a family having a registered case of pulmonary tuberculosis and were asked to write a medical and social history of the case. Before they did this they were given a schedule of study showing what information they must seek, and they attended a demonstration at which a case was presented in accordance with this schedule. Health visitors from the tuberculosis department introduced the students to the families, and the students consulted the departmental records of the cases. Each case-history was evaluated by me and the student was called to clarify points in the history and discuss the study. Occasionally he was asked to revisit the family or consult the records again.

The students on the whole did an excellent job, and some made instructive sketches to show the environment in which the families were living. Their interest was not confined to writing the medicosocial case-histories: where necessary they examined the sputum of patients and contacts, and took the contacts to the tuberculosis clinic for screening, Mantoux testing, and B.C.G. vaccination. A few patients who had defaulted from the clinic were persuaded by the students to revisit it for the usual check-up. Some of the students, going beyond their task, visited the neighbouring families to find out whether there were other cases of tuberculosis and what was being done for them.

I am grateful to Mrs S. B. Nayar, medical social worker of this department, for helping in the preparation of the schedule of family study, and to Prof. A. Leslie Banks, W.H.O. visiting professor in social and preventive medicine at this college, for his suggestions and encouragement.

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[1] World Health Organisation Conference on Mental Health, Helsinki. Abstr. *J. Ind. med. Ass.* 1959, 33, 196.
[2] Gour, K. N. *Ind. J. publ. Hlth,* 1958, 2, 40.
[3] Vengsarkar, S. G. *ibid.* p. 245.
[4] Patnaik, K. C., Holmes, E. M. *ibid.* 1959, 3, 269.
[5] Prasad, B. G. *J. King George's med. Coll. clin. Soc.* 1959, 42, 1.

Public Health

MILK COMPOSITION

An interdepartmental committee was appointed in May, 1958, under the chairmanship of Dr J. W. Cook, vice-chancellor of Exeter University, "to consider the composition of milk sold off farms in the United Kingdom from the standpoint both of human nutrition and of animal husbandry and to recommend any legislative or other changes that may be desirable." Its report was published last week.[1]

LEGAL DEFINITION

The committee finds that the definition of milk in the Food and Drugs Act (1955) is inadequate in relation to milk composition. The suggested statutory definition is:

> 'Cows' milk' means the secretion, excluding colostrum, which can be gained by normal milking methods from the lactating mammary gland of the healthy, normally fed cow.

RECOMMENDATIONS

The committee's main conclusions and recommendations are as follows:

Because milk is important in the human diet particularly by virtue of its content of solids other than fat (referred to collectively as S.N.F.), the consumption of milk S.N.F. should be maintained and, if possible, increased. Small changes in the fat fraction of milk are less important nutritionally than changes in S.N.F. The evidence of a link between either atheroma or ischæmic heart-disease and the consumption of milk fat, though suggestive, is not conclusive, and much research into the problem is urgently needed.

Both the fat and S.N.F. contents of milk have been falling gradually over the past thirty years in England and Wales, though there has been little change in Scotland. The decline in S.N.F. may continue unless steps are taken to arrest it, but most milk producers could improve the composition of their supply by changes in herd management if they were given the incentive.

The dairying industry therefore should aim not only to *maintain* but also to *improve* the S.N.F. content of liquid milk, and both statutory and marketing means should be used to this end.

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[1] Milk Composition in the United Kingdom. Cmnd. 1147. H.M. Stationery Office. 1960. Pp. 92. 5*s*.

Milk should continue to be sold as it comes from the cow, except for separated and other special grades, which should be clearly labelled and controlled. As a first step towards improving the quality of milk the marketing boards in Great Britain should pay less than the normal price for milk which is deficient in S.N.F. If this proposal is adopted the composition of milk from individual farms must be tested regularly by the dairy or depot to which it is first consigned.

Fixed legal minimum standards for fat and S.N.F. contents of milk would protect the consumer. The present standards are designed to ensure that milk is genuine, but they do not prevent the sale of genuine milk of low composition. The fat and S.N.F. contents should continue to be the criteria used for both legal and marketing purposes, and consideration should be given, within ten years, to prohibiting the sale of whole milk containing less than 3% fat or 8.5% S.N.F. The Hortvet test (for freezing-point depression) should, with certain provisos, be accepted legally as proof of addition of water to milk samples. Abstraction of fat from milk intended for sale as whole milk should be made a specific legal offence.

Milk recording should cover S.N.F. as well as fat content, because it is important to have details of the S.N.F. performance of individual animals if milk producers are to manage their herds to the best advantage. As soon as adequate information is available, S.N.F. records should be included among the data considered in the selection of bulls for artificial insemination. Licences for bulls of the dairy breeds should be refused in the absence of satisfactory records, and a new category of superior or premier grade should be introduced to include a minimum S.N.F. performance.

Diphtheria in Derby

A girl of 11 who lived in the Castle area of Derby fell ill with tonsillitis on Aug. 19. All throat swabs proved negative for diphtheria, but she died on Sept. 1 and the cause of death was established as myocarditis due to diphtheria. On Sept. 8, her brother of 13 was admitted to hospital with diphtheria and another brother was admitted as a carrier, and next day her mother and father were also admitted as carriers. On Sept. 10 a girl of 4 and on Sept. 14 a boy of 9 also living in the Castle area went into hospital with diphtheria. By Sept. 23 one other carrier had been identified and two cases of "diphtheroids". Virulence tests were being performed. None of the children with diphtheria and none of the carriers had been immunised.

Bovine Tuberculosis

An order made this week by the Minister of Agriculture declares the whole of England to be, from Oct. 1, an "attested" area in which all herds are tested for freedom from tuberculosis.[1] Scotland and Wales became attested areas last October. During an informal ceremony at the Ministry on Sept. 26, the Minister, Mr Christopher Soames, said the completion of the eradication plan was a considerable achievement brought about by intimate cooperation between the Government veterinary services on one side and the farmers and private veterinary surgeons on the other. Mr J. W. Salter Chalker, chairman of the animal health committee of the National Farmers' Union, hoped that a similar attack could now be made on other diseases—notably swine fever and contagious abortion.

First-aid in Factories

In future those nominated under the Factories Acts to be in charge of first-aid boxes in factories with more than 50 workers will have to be registered nurses, enrolled assistant nurses, or holders of a certificate of first-aid issued within the previous three years by a designated training organisation. An Order[2] to this effect will come into force on July 1, 1961, but until the end of 1962 a person shall be deemed to be properly trained if at any time in the ten years preceding the date when the Order was made (Sept. 13, 1960) he has held a certificate in first-aid issued by a training organisation.

In England Now

A Running Commentary by Peripatetic Correspondents

THE Borough Surveyor thought that three people were buried there. Only three names were carved on the solitary tombstone that stood in the way of his scheme to widen the corner by the chapel. There had been too many fatal accidents to leave it any longer. All he wanted to do was to chop off a triangle of land which he thought must have been part of the highway before the footpath was laid in Victorian times. Although nobody locally seemed to care, we got a licence from the Home Office to open the marked grave and move any human remains to the public cemetery. The Borough Surveyor thought it would be all over by breakfast time, but sent me an invitation. Medical officers of health are supposed to do their best for the safety of exhumations, so I went along.

The grave was 120 years old and contained a lot of babies' bones as well as the three adult skeletons. We put them all carefully into new caskets and sent them off to the cemetery. Then the soil slipped a bit and we realised that there were more on either side. We filled in the grave and summoned a full-scale conference on what to do next. The new road surface was going to be 3 ft. lower than the old footpath, and claims were coming in from the electricity board, the gas board, the water department, the Post Office telephones, and the drainage staff, all to lay their weird paraphernalia under the new highway line, and the usual right to dig it up again whenever they pleased. We reckoned that they might get well down into the grave levels, and we dare not risk a scandal. Nobody knew how many people had been buried in that strip of land over 100 years ago: the chapel registers were no help. The Borough Surveyor thought there might be three or four more to move, so up went the screens again, and the single-line traffic: the workmen started to dig in odd spots. When the first day yielded results scattered all over the site, we were faced with no alternative but to settle down for the summer and deal with the area like an archæological excavation.

We got out 134 bodies all told. They were not without medical interest. A couple of dozen had been buried in quicklime: smallpox, cholera, and typhus were common in the town in those days. One skeleton had no head, and another had its skull stove in. Adult teeth were very good on the whole, and we did not see much evidence of rickets. Some of the graves contained as many as 7 adult skeletons laid one on top of another, with odd bundles of infant bones tucked around their feet. Not a sign of wedding rings, and the only trinket was a little silver medallion commemorating the accession of William IV and Queen Adelaide. The site is now filled in, the lamp-posts up, the tarmac laid, the white lines painted, the double-deckers rumble by. I can only hope that the 134 forgive us for disturbing their rest. We did not like it either.

* * *

Gently it slithered through my letter-box. "Depression", it announced on the front (all my advertisements seem to say this now) and within snuggled a slim provocative little disc which, at 33 per minute, offered a moving dialogue between an inquisitive G.P. and a calmly instructive Consultant Psychiatrist. Some good straightforward facts and a wonderfully oversimplified classification filtered through two short sides of synthetic conversation, after which the G.P. presumably went his way rejoicing and cured everybody. But at least no excessive claims were made and (unlike some recent advertisements) a wise limit was set on which depressions the G.P. should treat and which he should send to a Consultant.

It is not this inoffensive record, but the future prospect that appals me. At first as a gimmick it will be popular, then people will realise that you can read things more quickly than playing them over *and*, if you like, listen to Beethoven at the same time. Then the discs will need to sustain themselves with gimmick upon gimmick. "Special offers" perhaps will be announced at some point during the playing, some firms may vocalise theirs, others trying blank-verse. Listening to them as they come will be a compulsive ritual just to find out what they are up to this morning—and remember, you can't flick a record over like a booklet It means sitting there for $9^1/_2$ minutes or else trying to decipher the gabble at 45, which probably plays hell with the stylus

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[1] *Times*, Sept. 27.
[2] First-aid (Standard of Training) Order, 1960. S.I. 1960 no. 1612.

I suppose the thing is useful for people who have failing vision or who cannot read, but I can't say it brightened my morning

* * *

I have been offered the following translation of a Russian article

Hard fall out symptoms in area of autonomic nervous system as a later consequences after poliomyelitis

" Till now poliomyelitis was considered as a desease of spinal cord by causing a damage in prior horns of spinal cord and subsequently the clinical symptoms shows a diminished or output of motorical innervations in various groups of muscles or in uper or lower extremities according to the localisation and extension of pathological substratum Contrary this article proofs that not only the motorical system is damaged but throughout an appropriative autonomic nervous system can be devastated by an extended pathological substratum of poliomyelitis

" According to these insufficiencies we must concluse that pathological substratum by its extension damaged not only a prior horns, but in neighbourhood dislocated a side cords as a higher centers of autonomic nervous system This an explanation of nine abortus and a great œdemas of lower extremities from which organs (an uterus and lower extremities) has their higher centers of autonomic nervous system in region where poliomyelitis made a biggest devastation in area of lumbar I-V

" Such an observation in literature till now was not confirmed or noticed."

I'll say it wasn't!

* * *

" Resourcefulness is a dominant gene in my family," said Ananias, levering Boyd's *Pathology* out of the bookcase to see whether the gin bottle was behind it " A prize example was my cousin Arthur He landed in the United States without a penny and six weeks later he was worth $5000—at any rate that's what the police were offering for him I am not therefore downcast because some abandoned bodysnatcher has finished the gin I shall simply put some adhesive plaster over my antecubital fossa and lie on a couch in the blood-transfusion centre Light refreshments will be brought to me by ravishingly beautiful nurses—they keep the prettiest ones there to bait the trap—and I'm all set for a date at the Palais, if you've got any money Incidentally, *have* you got any money ? "

" Yes thank you," said Macabre, the pathologist, " and don't tell me your Chief has sent you here to request even more bottles of blood Is he keeping up with the Draculas or something ? "

" My Chief, the Laird MacGrolloch, was muttering about Flodden Field last night When he does that, the next patient he broaches needs a refill, even if he, or she, has only had their ears pierced So please attend to my order now before the flowers of the forest are a' wede awae, and for goodness' sake ensure that your tame ghouls get the bottles from the correct bin, because I heard of one patient who received some from a Chinaman He became *ipso facto* a blood-brother in the Mildewed Lotus Tong, and every time Tong warfare broke out he had to have police protection."

" I don't care whether it's for the flowers of the forest or Bonnie Prince Charlie," said Macabre crossly, " the stuff costs the country about £30 a pint You could," he added hopefully, " be dead and buried for less than that "

" My cousin Arthur nearly was," replied Ananias " He's suing the pathologist for giving him cirrhosis of the liver Seems he forgot to crossmatch the blood for the various brands of gin "

* * *

APOTHECARIES ABANDONED

To ease the task of future pupils
  Let grains ingrain'd no longer be
Abandon minims, have no scruples
  Come, take a drachm—no, dram—with me

Letters to the Editor

OUR POOR THAMES

SIR,—Compared with Our Poor Thames the Tone is an insignificant stream with an average daily flow in summer of about 15 million gallons but suitable in many places for alfresco bathing It drains a district heavily stocked with animals and receives treated and untreated human sewage Since 1955 this laboratory has examined daily or weekly samples of water from the Tone for *salmonella spp* using both the Moore swab and (less often) a filtration method Our results have been thus

Year	*Samples*	*Isolations*
1955	82	13
1956	134	6
1957	60	0
1958	32	1

During this period many people have bathed at or below the sampling point It is impossible to say that no-one has acquired an infection from bathing during this period, but this laboratory (to which almost all the bacteriological specimens from this neighbourhood are sent) has seen no evidence of such infection

I hesitate to mention my personal experience because I do not want to be accused of foolhardiness At one time I lived on the banks of the Tone and in hot weather my family bathed in it regularly During one hot spell my wife, my daughter, my spaniel, and I bathed every evening for about a week At this time *Salmonella thompson* could be found in every Moore swab put in the river at our bathing place and for 8 miles upstream None of us made any particular effort to keep the water out of our mouths but none of us had any symptoms of illness I did not examine our fæces bacteriologically as I should have done

There is not much evidence on the dose of salmonellæ necessary to produce disease in man, but such as there is suggests something of the order of 10^6 organisms[1] (the figure for *Salm typhi* is probably much less) Using a filtration method of isolation (suggested to me by Dr G J G King) some rough estimates of the numbers of salmonellæ present in the Tone water on several occasions gave figures of 10 organisms per litre or less I have no doubt that salmonella infections can be acquired by bathing in rivers—but very rarely I would, however, avoid bathing immediately below a sewage outfall

Public Health Laboratory,
Taunton.

J A BOYCOTT

ECZEMA VACCINATUM

SIR,—Dr Reynolds does well to remind us, in his article last week, that this infection often proves fatal in infants and can be prevented, but he does less than justice to his own countrymen's work on the subject, for in quoting eighteen references he mentions only two British I append a list[2–14] of some of the more important British papers on Kaposi's varicelliform eruption

McLachlan and Gillespie[2] described a severe outbreak of vaccinia infection in a Glasgow children's ward, and Brain and

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[1] McCullough, N B , Eisele, C W *J infect Dis* 1951, 88, 278
[2] McLachlan, A D , Gillespie, M *Brit J Derm* 1936, 48, 337
[3] Brain, R. T , Lewis, B *ibid* 1937, 49, 551
[4] Whittle, C H , Lyell, A , Miles, J A. R., Stoker, M. G P *ibid* 1950, 62, 195
[5] Leverton, I C S , Whitlock, F A. *ibid* 1949, 61, 170
[6] Anderson, T *ibid* p 157
[7] Bettley, F R. *ibid* 1940, 52, 222.
[8] Brain, R. T *Aust J Derm* 1954 2, 109
[9] Brain, R. T , Dudgeon, J A., Philpott, M. G *Brit J Derm.* 1950, 62, 203
[10] Brown, W H *ibid* 1934, 46, 1
[11] Ellis, F A. *ibid* 1936, 48, 524
[12] McLachlan, A. D *ibid* 1934, 46, 8
[13] Somerville, J , Napier, W , Dick, A. *ibid* 1951, 63, 203
[14] Varley, R., Kletz, T *ibid* 1949, 61, 166

Lewis[3] succeeded in producing lesions with blister fluid by inoculating a rabbit's cornea Full virus studies were published for the first time in this country[4] in 1950, and in a review of 58 cases of Kaposi's varicelliform eruption in the literature 27 were found to be due to vaccinia and 11 to herpes-simplex virus Other viruses such as the influenza virus might produce the same clinical picture[5] and could account for some of the remaining 20 cases in which the virus was not traced. Anderson,[6] to avoid confusion, suggests the name "virus pyodermia" because more than one virus is implicated

Vaccinia infections of this type can occur in adults and, as Dr Reynolds suggests, atopic eczema is not the sole portal of entry for the virus Of 3 adults I have seen with vaccinial lesions of this type one was an army recruit whose eruption appeared, about ten days after his primary vaccination, not on eczematous lesions, because he had none, but on chronic patches of psoriasis He was very ill for a week or two but survived

Cambridge. C HOWARD WHITTLE

TROLLEY-SETTING

SIR,—Dr Behr (Sept 17) wonders whether General Nursing Council examiners can be persuaded to accept new techniques for dressing wounds In Sunderland many of the methods advocated by him have been used for two years [15–17] Bowls and gallipots are not used for dressings and each dressing is done from an individual pack, this eliminates the old type of trolley setting

Dr Behr need have no misgivings All G N C examiners who have seen this method have accepted it at once and have welcomed it as an improvement in nursing technique

Central Laboratory,
Royal Infirmary, Sunderland. J F WILSON

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—I should like to thank Dr Lawrence for his reply (Aug 27) to my letter of Aug 13 His criticisms are welcome but not unexpected

I fully realise the theoretical dangers that a syringe which is sterilised only once every three months is liable to become contaminated I have always assumed that the small quantity of preservative that is mixed with all types of insulin will maintain the sterility of the plunger and inner surface of the barrel of the syringe as well as the needle As the syringe is never rinsed in spirit or water, a trace of the preservative will remain constantly in the syringe and needle Whatever the theoretical dangers I have no doubts about the practical safety of the method. Seventeen years' trial involving over six thousand self-administered injections without ever a trace of inflammation seems sufficiently satisfactory a result to suggest that other diabetics might like to experiment along the same lines

Dr Lawrence considers that many patients would not observe the "no-touch" technique which I recommend for the needle, but I think he is unduly pessimistic In my experience, the most likely time for contamination is in assembling the syringe and needle after sterilisation by boiling If a diabetic can perform this manœuvre correctly, there is no reason why he should not be able to avoid touching the needle during his daily injections I can only remember making this error twice

I am afraid Dr Cuddigan (Sept 3) must have misread my letter concerning the use of surgical spirit. The syringe is never placed in spirit, nor is it rinsed in water except immediately before resterilisation when the old needle becomes too blunt for comfort and is replaced by a new one

Mr Merryweather Shaw rightly draws attention (Sept. 3) to an omission I made in describing the loading of the syringe with insulin. It is of course important to inject air into the inverted bottle before withdrawing insulin in order to avoid producing a vacuum in the bottle, but the risk of contamination appears to be of theoretical rather than practical significance Mr Shaw's use of sterile, disposable, plastic syringes may sound somewhat extravagant, but Dr Lerman (Sept 17) points out that these syringes can be produced at a very low cost However, as a glass syringe should last several years (I am still using my fourth), the cost of plastic syringes will have to be extremely low to make their use on a large scale an economic proposition

Finally, I was delighted to read Dr Wauchope's letter (Sept 10) She obviously treats her injections of insulin with an even greater care-free abandon than I do I have never quite reached the depths of non-sterility that she proclaims as I always swab with spirit the rubber cap of the bottle as well as the site selected for injection, but her technique (or lack of it) over many years has given complete satisfaction I hesitate to accept her theory that diabetics develop an immunity to their own contaminants In theory there is great risk of infection by using a technique that involves such infrequent sterilisation of one's syringe, but apparently this does not manifest itself in practice

Queen Elizabeth Hospital,
Khormaksar, Aden. F STEPHEN CARTER

VIRUS TUMOURS OF MICE

SIR,—After reading your occasional survey[1] we should like to record that one of our observations[2] still awaiting explanation was as follows

About 40% malignancy—i e, different tumours and stem-cell leukæmia—developed among F_1 progeny of some low-malignancy strain mice, originally free of leukæmia, if mothers were inoculated subcutaneously with massive doses of A K R. lymphocytic leukæmic cells in their late pregnancy, and the same inoculations of pregnant A K R mice, causing the death of mothers in acute leukæmia, failed to alter the fate of their A.K R–F_1 progeny

Although these preliminary results await confirmation, we suggested that if these induced tumours or leukæmias in the low-malignancy strain were caused by a virus, it would be difficult to understand the absence of its effect (cf Laterjet[3]) in the original A K R -leukæmia strain

Department of Medicine,
University Medical School,
Szeged, Hungary

E KELEMEN
M TENYI

DOUBTFUL PROGRESS IN PSYCHIATRY

SIR,—The difference of opinion between Dr Allchin (Sept 17) and myself is, no doubt, very largely semantic

What I believe the court to have requested, in the first place, is my advice in the form of a *practical recommendation,* in a specific case at a particular time, and if such a recommendation were to be made in the form of what I feel *ought* to be done (were it only possible to do so), I would not be assisting those who have sought my advice, in reaching a practical decision in that case and at that time I would, therefore, be helping neither the individual concerned, nor society, nor the authorities and officials whose responsibility it is to take some immediate and positive action, I would also be most liable to discourage further cooperation on the part of the latter, who could hardly be blamed if they were then to conclude that psychiatrists were unrealistic and unhelpful In my view, we would thus have defeated, ab initio, our own aims of achieving through the education of all those involved a better and more effective mental health service

This is, therefore, far from saying that I in any way underestimate the importance of the educational duty of the psychiatrist, as emphasised by Dr Allchin In fact, I too have long made it an invariable practice clearly to state the action, method of treatment or care, which would, in my

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[15] See *Lancet*, 1960, i, 661
[16] *ibid* Aug 13, 1960, p 353
[17] Thompson, M. E. *Nursing Times*, 1960, 56, 869

[1] *Lancet*, July 23, 1960, p 200
[2] Kelemen, E. 7th European Congress of Hæmatology, London, 1959
[3] Laterjet, R. Ciba Symposium on Carcinogenesis, pp 274–295 London, 1959

opinion, ideally be required but, unfortunately, that is most frequently something quite distinct from the practical recommendation for which I am asked Indeed, I may be fully convinced that a patient is in very great need of six months' rest in a beautiful climate, but I—and he—must needs compromise with some less satisfactory " solution ", and will most probably have to go on doing so in the foreseeable future, and, it may be, until the advent of the millennium

Bransgore, Hampshire R H AHRENFELDT

ÆTIOLOGY OF ECLAMPSIA

SIR,—Moses et al [1] claimed that the development of pre-eclampsia in a patient both of whose adrenals had been removed, apparently for Cushing's syndrome, is " further evidence that the adrenal steroids do not play a major role in the causation of pre-eclampsia "

I would respectfully submit that the case described was not pre-eclampsia but chronic hypertension Her blood-pressure at the beginning of pregnancy was 170/110 mm Hg At about the 6th month it was 220/110 when she had headaches, nausea, vomiting, malaise, and albuminuria, which might well be attributed to a superimposed pre-eclampsia Throughout her pregnancy, however, she had been receiving hydrocortisone Is it certain that this had nothing to do with the rise of blood-pressure, œdema, and albuminuria, thus stimulating pre-eclampsia or actually causing it?

Moses et al quote Cohen [2] as reporting the onset of pre-eclampsia in a woman who had Addison's disease But this patient also was receiving adrenocortical therapy throughout her pregnancy

Both these cases must therefore be rejected as evidence against the role of the adrenal steroids in the ætiology of pre-eclamptic toxæmia

Wollstonecraft,
New South Wales F J BROWNE

THE VERY DEAF CHILD

SIR,—Your annotation of Sept 17 must not go unchallenged, for some of your statements may mislead those who have had little experience of the deaf child and its problems

The Board of Education Committee's classification, though written in 1938, has not yet been superseded for the good reason that no-one has been able to formulate one with less defects and more practical advantages As with all definitions, no harm can come from a theoretically poor classification provided the parameters involved are understood, and educational and administrative elasticity is maintained The National College of Teachers of the Deaf has recently given time and thought to this classification, and members to whom I have spoken do not regard it as sacrosanct, but do not minimise the difficulties involved These difficulties are due to an inability to define, in any mathematical way, such terms as " partial deafness ", " good lip-reading ability ", " spontaneous speech ", and " adequate auditory stimuli " When experimental methods and applied psychology have given us better means of measuring these concepts, we may be able to rewrite the existing classifications

Damnation of schools for the deaf in your last sentence is unjust It is true that there are bad schools but there are good ones too, and the same range of quality is found in schools for the deaf as in schools for normal children While heartening results have been achieved in recent years by the treatment of many children as partially deaf rather than as grade III, it must not be forgotten that there are still oral failures in the best schools, and that there are children who do not learn to speak at all, despite all the advantages of an early start and every possible help Teachers of the deaf are as aware of their failures as, for instance, is the honest surgeon of his recurrent hernias or the otologist of his unsuccessful fenestration operations, but these failures do not make admission to hospital and operative treatment " unthinkable "

It is very right that recent results achieved by auditory training, in the case of young children, should be given wide publicity, but it must be remembered that there has not yet been any suitable statistical survey of the long-term effect of this early training to show that lip reading, which incidentally was not mentioned in your annotation, can be discarded as an educational method, or that the failures of auditory training are unknown.

Eye, Ear and Throat Hospital,
Murivance, Shrewsbury E N OWEN

PORPHYRIA

SIR,—Nazzaro, Topi, and Venerando [1] suggest that the form of porphyria designated porphyria cutanea tarda should more appropriately be named mixed or combined porphyria on the grounds that many of these patients present both cutaneous lesions and the systemic symptoms characteristic of acute porphyria They also comment that in some instances there is evidence of familial incidence whilst in others this is wanting even though relations are available for examination

Dean and Barnes [2] have shown that the classical intermittent acute porphyria (I) can be differentiated on biochemical grounds from an apparently mixed form for which they suggest the name porphyria variegata (II) Both these forms are based on constitutional predispositions which are inherited according to the mendelian dominant rule with no sex-linkage Porphyria variegata is a specific entity and should not be named or regarded as a mixed or combined form Barnes [3] has also reported the prevalence in Bantu subjects (indigenous Africans) of a cutaneous porphyria (III) in which there is no tendency to acute episodes and which can be distinguished from erythropoietic (congenital) porphyria There is no satisfactory evidence for an hereditary basis for this form In summary, the distinguishing features of these three forms are

(I) *True acute porphyria* —Raised urinary excretion of δ aminolævulic acid and porphobilinogen is the most constant characteristic This sometimes occurs in latent (presymptomatic) cases, is exaggerated during the acute episodes, and persists for long periods after recovery Stool porphyrins are sometimes normal, sometimes slightly increased, but, according to present limited experience, never markedly increased

(II) *Variegate porphyria* —The most constant biochemical anomaly is a large increase in stool porphyrins which is found irrespective of the clinical status of the patient and has been observed in asymptomatic members of affected families δ-aminolævulic acid and porphobilinogen are excreted in excess during acute attacks but diminish with recovery and are almost invariably normal during remission from attacks Porphyrin is sometimes normal in the urine during remission, but traces or larger amounts can usually be detected

(III) *Cutaneous porphyria* —Urinary porphyrins (mainly uro-) are present in excess in freshly passed urine This is most pronounced when skin lesions are active but slight excesses have been observed some years later when scarring was the only evidence of former lesions δ-aminolævulic acid and porphobilinogen are usually normal but slight increases have been found when uroporphyrin excretion is very high Stool porphyrins are normal in about half the patients and only slightly raised in the remainder

Many cases of porphyria have been reported in Italy, Spain, and France, both cutaneous and acute symptoms being mentioned, but very little of this literature is available to us *If, as may be inferred from the statement by Nazzaro et al , many* of these patients have variegate porphyria, the interesting possibility arises that while true acute porphyria has originated in Northern Europe (Lapland is suggested by Waldenstrom [4]) the variegate form may have been established in the south. Both these hereditary types have been carried by travellers and migrants to other countries in the world The picture is complicated by the probably acquired cutaneous porphyria

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1 Moses, A M , Lobotsky J Lloyd C W *J clin Endocrin* 1959, 19, 987
2 Cohen, M. *Arch intern Med* 1948 81, 879

1 Nazzaro, P , Topi, G C , Venerando, A *Policlinico*, 1958, 56, 1213
2 Dean, G , Barnes, H D *S Afr med J* 1959, 33, 246
3 Barnes, H D *ibid* p 274
4 Waldenstrom, J *Acta genet* 1956, 6, 122

(iii) Alcohol and arsenic (anti-syphilitic treatment) figure prominently among suggested ætiological factors,[5–7] but these probably include liver noxa of many kinds and contributory liver damage consequent upon earlier illnesses cannot be ignored. Such cases may, therefore, arise sporadically. Exposure to sunshine is probably an evocative agent for the skin lesions in groups II and III, but this has been included with alcohol and heavy metals as a primary ætiological factor by Ippen.[8]

Accurate differentiation of these forms, especially between II and III, is not merely an academic exercise. Patients in groups I and II are susceptible to acute episodes which might end fatally, while, according to present experience, those in group III are not. There are on record many instances of these acute manifestations being precipitated by the use of barbiturates, including thiopentone for anæsthesia, and other drugs. It is thus very desirable that these cases should be fully investigated.

H. D. BARNES
Johannesburg. L. C. TURCHETTI TUCCIMEI

VOLUNTARY ISOLATION

SIR,—Having had close experience of 85 separate groups at work in the Antarctic over the past 11 years I was interested to read an extract from your annotation[9] on this subject.

Only three weeks earlier I had written a letter to one of our scientific advisers in England in which I said that ability and qualifications were "75% of the necessary background to successful living on a base. It does not matter how active and strong and cheerful a man is, if he cannot keep the engines running, or the base on the air, then the others will have no time for him and he himself will lose his self-respect, a state which readily gives rise to neurosis." This bears out the statement that "The over-riding criterion is that a man should be efficient at his job." We have also had a few, fortunately very few, perfect examples of the "type of newly graduated scientist, unworldly but intellectually arrogant."

J. R. GREEN
Secretary,
Falkland Islands Dependencies Survey.

Port Stanley,
Falkland Islands.

PSYCHOANALYSIS

SIR,—In the preface to the 1960 edition of *Clinical Psychiatry*, Dr. Mayer-Gross complains that his detailed critique of psychoanalysis in the introduction to his book in 1954 was not challenged. Two reasons at once come to mind.

(1) Readers of psychiatric literature, perhaps more than those in other fields, are very selective, and generally read only the publications of kindred minds. I think this would also itself explain his contention that the attempted re-export of psychoanalytic teaching from America into Europe was "largely in its original naive form." By 1954, the body of psychoanalytic work pursued in America is greatly modified in form from orthodox psychoanalysis, although this still had its champions, perhaps proportionately more in England than in America.

(2) The grounds for criticism were also ancient in derivation. In fact, in the chapter on the psychological treatment of schizophrenia in the 1960 edition, Speer (1927) is still quoted as having arrived at the judgment that psychoanalytic methods leave the patient unaffected by treatment.

American psychiatry today is greatly influenced by the works of Harry Stack Sullivan, Frieda Froom-Reichmann, Clara Thompson, and Carl Rogers, to mention a few, none of whom are even mentioned in his references.

Littlemore Hospital,
Oxford. M. J. ORTEGA

SHORTAGE OF DIETITIANS

SIR,—We are very interested in your annotation of Sept. 17 on the shortage of dietitians. I write, however, to point out that integrated courses of training for dietitians lasting three years have already been established.

A course of three years, including six months at a recognised hospital dietetic department, has been in existence for some years at the Battersea College of Technology. The requirements for entry include chemistry and either physics or biology (or zoology) at advanced level in the General Certificate of Education. A four-year integrated course has just been instituted at the Leeds College of Technology, and candidates with advanced-level chemistry and biology may be admitted directly to the second year—that is, for a three-year course.

B. J. JAMIESON
London, S.W.3. Secretary, The British Dietetic Association.

*** We are grateful to Miss Jamieson for this information, and also for sending us a copy of the report[1] of a fact-finding committee set up last year by the British Dietetic Association. 740 questionnaries were sent to dietitians, and in the 391 returned the great majority expressed dissatisfaction with the present situation. Frequent comments were made about poor salaries in the National Health Service, the length of training required, the lack of status in hospitals, and the misuse of dietitians' services.—ED. L.

CONTROL OF HOSPITAL CROSS-INFECTION

SIR,—I was interested to read the article of Sept. 10 by Professor Elek and Dr. Fleming on a new technique for the control of hospital cross-infection using BRL 1241 in a maternity unit, because I described[2] a rather similar technique in 1956 by which a successful attempt was made to reduce nasal infection in a residential nursery which catered for 20 children up to 3 years old.

The infection had been present for many months but responded in an amazing way to the use of 'Aeryl 4' in an electrically operated 'Phantomyser' spray. The results of this were assessed clinically, a successful result being shown by the disappearance by the 24th day of nasal discharge in 14 of the 17 babies involved.

The conclusions I drew from my investigations were:

(1) The infection had been maintained by infection of babies shortly after entering, and continual reinfection thereafter.

(2) The effects of the spray were mainly mechanical—i.e., in the formation of droplet nuclei carried down from the atmosphere to the floor.

(3) Although this was not an ideal method of dealing with the situation it was at any rate successful in this particular instance.

I was sorry to learn that the Medical Research Council had not found my method successful in dealing with infection in residential nurseries run by Dr. Barnardo's, though I suspect that the method they adopted entailed the use of a vaporiser instead of an atomiser.

I hope that the article by Professor Elek and Dr. Fleming will stimulate further interest in a method which I feel could play an important part in dealing with the problem of cross-infection in hospitals.

Civic Centre,
Dagenham. J. ADRIAN GILLET

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[5] Brunsting, L. A. *A.M.A. Arch. Derm. Syph.* 1954, 70, 551.
[6] Berman, J., Bielicky, T. *Dermatologica*, 1956, 113, 78.
[7] Tappeiner, S. *Wien. klin. Wschr.* 1953, 65, 143.
[8] Ippen, H. *Berufsdermatosen* 1959, 7, 256.
[9] *Lancet*, 1960, i, 1231.

[1] *Nutrition*, 1960, 14, no. 2.
[2] *Med. Offr*, 1951, 86, 5.

HYOSCINE ADDICTION AND INTOXICATION

Sir,—Hyoscine was used extensively for motion sickness in the Forces from 1942 onwards, and was first sold to the public in May, 1947, as ' Kwells ' The toxic effects of hyoscine may include confusion, a muttering delirium, or stupor deepening to coma

A 54-year-old housewife was admitted to hospital on Aug 14, 1959, in a confused state She was agitated and frightened, and she was seeing " thin, horrid slug-like creatures with golden heads coming out of the floor " She was disorientated in space and time, and it was very difficult to hold her attention There was clouding of consciousness, and her thinking was so confused that further history-taking was impossible

Her husband stated that the trouble started after hysterectomy six years previously, when she began to feel nervous and depressed and to suffer from headaches for which she took a variety of tablets, mostly, he thought, sedatives She had been buying kwells regularly for about two years to help her in travelling, but recently had been taking an increasing number of tablets even when not travelling Six weeks before she had been discharged from another hospital where she had had a course of electroconvulsion therapy for a depressive illness After this she had increased her consumption of kwells to 12 tablets daily

Her face was leaden-grey, and her skin and mucous membranes were dry The pulse was full and bounding, and the blood-pressure 160/90 mm Hg The pupils were dilated and fixed and all reflexes sluggish There was no rash or skin disorder and the bladder was not distended After admission she was given a course of intramuscular ' Parentrovite ', prophylactic penicillin, and copious fluids The atropine-like symptoms responded to neostigmine bromide 15 mg three times a day

Routine blood and urine investigations were normal An electroencephalogram on the third day after admission showed " repeated episodes of theta activity which suggest organic disturbance This appears to be in the deeper brain areas but is symmetrical on both sides which suggests this is a toxic rather than a space-occupying disturbance " The record was repeated fourteen days later and showed no abnormality

The patient remained confused and disorientated for five days after admission, but next day she was no longer hallucinated, and was more cooperative, although she still showed some clouding of consciousness and incoherence of thought Memory for recent events was impaired and there was a tendency to confabulate After a further seven days she was completely rational and capable of giving a coherent history

She had first started to take increasingly large doses of barbiturates after the hysterectomy six years before Several times she changed her doctor after being refused the quantities of drugs she wanted, and at times she used other patients to obtain barbiturates for her About two years ago she started taking kwells, at first for travel sickness, but later because they eased the tension she felt when she had to meet other people In the few months before admission to hospital she was increasingly depressed and had had frequent headaches She found it necessary to increase the number of tablets until shortly before admission she was taking 12 daily Her degree of dependence was such that on one occasion, at a weekend, her husband had to tour the local chemists' shops to obtain fresh supplies for her

Psychiatric evaluation indicated that she had a chronic anxiety hysteria with an overlay of neurotic depression

Three weeks after admission she showed no signs of toxicity, and although she had been much brighter, her depression returned, and she became irritable and hypochondriacal She was given a course of E C T which cleared the depression She left hospital for weekend leave on Oct 2, 1959, and failed to return

In spite of the sedative action of hyoscine, we have been unable to trace any recorded cases of addiction, and this case is reported to emphasise that substances other than the usually recognised drugs of addiction may lead to habituation in susceptible personalities

There has recently been an increase in addiction to non-scheduled drugs—for example, to phenmetrazine (' Preludin '),[1 2] and to carbromal, chlorodyne, and phenmetrazine [3] Many are in favour of restricting the sale of all such drugs, and this has been done for phenmetrazine Douthwaite,[4] however, believes " we should think very carefully before recommending restrictions to legislators which would inevitably involve the practitioner in yet more work and which would do but little to protect a relatively small number of psychopaths ", and we subscribed to this view It would scarcely seem justified to restrict such a useful drug because of intoxication by addiction in a neurotic personality

Our thanks are due to Dr R Mackarness, of E Griffiths Hughes, Ltd , for his helpful advice

Whittingham Hospital,
Preston

P Harper
D P Oakley

PARKING AND THE DISABLED DRIVER

Sir,—When I committed my most recent parking offence by exceeding the time-limit plainly indicated on a sign obscured by a furniture van, the heart of a constable softened at my suggestion that he might care to push my wheel-chair the odd five hundred yards to the nearest car park, when next I ventured to visit the police station I had just called to settle a little matter arising from another recent parking offence

The disabled motorist is obliged to do his best to avo adding to the appalling traffic chaos, but his plight never obvious until he attempts to extricate himself fro his vehicle or shouts for help, the former often impossib and the latter liable to misinterpretation His need to fi a parking space close to the shop or house he wishes visit is far greater than that of the ordinary motorist

A discreet but easily recognisable car badge, issued, Dr Piper (July 2) suggests, by the Ministry of Pensio and National Insurance, would enable the police and th traffic wardens to identify the disabled motorist at glance and assist him to find a suitable place to disembark

Wilmslow, Cheshire

W H W Inman

CORTICOSTEROIDS AND RAISED INTRACRANIAL PRESSURE

Sir,—In the matter of corticosteroids and raised intra cranial pressure, it is surprising that so far only th negative aspects have been emphasised, and no attentio has been paid to the much more interesting positive side Thus, although it is undoubtedly true that prolonge steroid therapy,[5] or its sudden interruption,[6] may produc intracranial hypertension, the opposite is just as true an much more important—that is, intracranial hypertension due to the usual causes (space-occupying lesions o inflammatory processes), is favourably influenced b corticosteroids

In a series of tests in children (in whom hypertensive intracranial reactions are particularly severe and readily recognised) we found that 15–30 mg of prednisone per day (1) noticeably reduced or completely abolished the outstanding symptoms (headache, vomiting and nausea, confusion, and clouding or impairment of consciousness) within three or four days, (2) reduced to a variable extent such symptoms as ataxia,

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1 Silverman, M *Brit med J* 1959, i, 696
2 Bethell, M F *ibid* 1957, i, 30
3 Seager, C P , Foster, A R. *ibid* 1958, ii, 950
4 Douthwaite, A H *ibid* p 1161
5 Laurance, B M , Matthews, W B , Shephard, R H *Lancet*, 1960, i, 701
6 Dees, S C., McKay, H W *Pediatrics*, 1959, 23, 1143

papilloedema, and E E G abnormalities, within ten to fifteen days, and (3) induced a strong feeling of wellbeing The effects were at times so rapid and intense, especially in hypertension produced by tumours, that, both subjectively and objectively, the patient seemed to be almost completely cured. Naturally, in raised intracranial pressure produced by tumours, the improvement is only symptomatic and temporary it has, however, the advantage of making pneumoencephalography, ventriculography, and operation safer and easier In inflammatory hypertension corticosteroids not only give immediate relief of symptoms but also are useful therapeutically

C Fazio
M De Negri
V Grillo
E Tartarini

Clinica delle Malattie Nervose e Mentali
e Instituto G Gaslini, Genoa.

HEALING OF WOUNDS

Sir,—May I draw attention to the fact that thyroid medication in patients with breast cancer, after radical mastectomy, accelerates healing by producing more histamine in the skin?

These patients and patients with cancer of the female genitalia usually have a very low level of protein-bound histamine in the tissues [1] If thyroid is given by mouth in increasing doses with histidine monohydrochloride, the histamine content of the tissues is increased The skin of these patients was examined for histamine by Dr W S Feldberg at the National Institute for Medical Research [2] Wound healing in these patients proceeded quickly and satisfactorily and recurrences were prevented for many years [3-5]

Thyroid emulsion and histidine injected together into and around the breast tumours led to their recession and sometimes even complete disappearance.

The histidine monohydrochloride was supplied by Roche of Basle Further details will be published later

These investigations took place in St Bartholomew's Hospital, Rochester, and St Mary's Hospital, London

London, W 1

Alfred A Loeser

ARTIFICIAL INSEMINATION

Sir,—My letter of Aug 27 was a statement of fact that A.I D was not adultery. Dr Roberts' reply (Sept 17) is an expression of opinion on the ethics of A.I D , an entirely different kettle of fish.

Crediton, Devon.

L N Jackson

PRIMARY BILIARY CIRRHOSIS

Sir,—Dr Mackay (Sept. 3) suggests that primary biliary cirrhosis is an autoimmune disease He states "Thus there is evidence that primary biliary cirrhosis should be classified within the group of tissue-destroying immunopathies"

The evidence that Dr Mackay offers includes structural alterations in the liver, kidney, and stomach as noted in biopsies of these organs These alterations consist of "lymphoid-cell" infiltrates and "destruction of tissue" The accompanying photographs of the stomach and kidney appear to us to be non-specific gastritis and a small focus of chronic pyelonephritis

These non-specific alterations are frequently found in necropsy or biopsy material and, if one so desired, one could probably correlate them with virtually any unrelated disease process In a review of our four necropsy cases of primary biliary cirrhosis, for the period 1945–55, we found no morphological alteration that allows the conclusion that there is a "multi-system disease" or an "immunopathy"

James Homer Wright
Pathology Laboratories,
Massachusetts General Hospital,
Boston, Massachusetts

Benjamin Castleman
Wallace A Jones

HÆMATEMESIS AND MELÆNA

Sir,—I am grateful to Dr Chandler and his colleagues (Sept. 3) for their reference to my dissatisfaction over the radiological investigation of hæmatemesis, but I feel they do scant justice to the excellent work of Dr Cantwell who devised the ward technique and already has published reports [1 2] on two series of patients Dr Cantwell in his last paper recorded 82% correct results in 200 patients, and this figure is being maintained in a further series which will be published when it is large enough

Department of Diagnostic Radiology,
The United Leeds Hospitals.

A S Johnstone

TRIGEMINAL NEURALGIA

Sir,—The last three cases of true trigeminal neuralgia that have reached me have been associated with what I call the temporomandibular-joint syndrome, and each of the three cases has benefited from treatment of that condition

It is easy to diagnose a temporomandibular-joint abnormality when there is audible clicking of the cartilage, or when the joint itself is tender to direct palpation, but it is not very generally appreciated that there is a syndrome which arises from relatively trivial damage to a temporomandibular joint which itself can remain painless

My interest in the subject was first aroused by finding that almost always in cases of so-called atypical trigeminal neuralgia palpation of the deep aspect of the joint not only elicited the pain of which the patient complained but also resulted in his having an unusually uncomfortable day or two subsequently It seemed to me that the pain I elicited arose from the anterior head of the lateral pterygoid muscle, and, after discussing the matter with my orthopædic colleague Mr Denis Dunn, we began treating such cases first by injecting cortisone suspension into the muscle itself, and later (by analogy with the syndrome known as tennis-elbow) by injection into the temporomandibular-joint space. The results were rather mixed, but my present view is that the intra-articular injection is by no means easy and is not always successfully achieved, and my impression is that when the injection has proved easy and convincing the results have been equally satisfactory Intra-articular injection of cortisone for the clear-cut temporomandibular-joint lesion is of course routine practice in many centres, but I have not discovered any reference to the syndrome associated with a joint which remains painless throughout. In some undiagnosed cases of facial neuralgia the site of the rather elusive pain may be found to be the lateral pterygoid muscle, which is almost inaccessible above and behind and lateral to the maxillary tuberosity

In my experience these cases present with a history of pain which is localised most usually in the area superficial to the maxillary antrum but may sometimes be referred to the ear, the malar region, the angle of the mandible, or even the neck, but whatever the site complained of, the pain can be elicited by palpating the lateral pterygoid

In the three cases of apparently true neuralgia referred to, the trigger zone was in the maxillary division of the fifth nerve, and palpation of the lateral pterygoid on the affected side merely produced pain but did not provoke a neuralgic paroxysm, the frequency and severity of the paroxysms decreased progressively when the joint-space was injected weekly

I do not suggest that all cases of paroxysmal facial neuralgia are caused by the temporomandibular-joint

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[1] *Brit med J* 1954, ii, 1380
[2] *J Physiol* 1954, 126, 256
[3] *Brit med J* 1955 ii, 143
[4] *Lancet*, 1955 i, 491
[5] *J int Coll Surg* 1958, 29, 337

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[1] Cantwell, D F *Brit med J* 1957, ii 941
[2] Cantwell, D F *Clin. Radiol* 1960, 11, 7

syndrome, but I have the suspicion that at least some of my own patients who have in the past sustained alcohol injections had no more than a minor traumatic derangement of the mandibular joint

I should like to acknowledge that in arriving at the conclusions which led to the treatment I am adopting at present I was helped and guided by my colleagues Dr A B Pollard, Mr J B M Green, Mr Denis Dunn, and in my own department by Mrs E B Kendall

Essex County Hospital,
Colchester

MICHAEL FROST

OBSTETRIC FLYING-SQUADS

SIR,—Thank you for your comments on my letter of Sept 3 While agreeing that early blood-transfusion may be advisable in some cases of hæmorrhage, I notice in the report on maternal deaths,[1] which you quote, that there is nothing to suggest that any of the mothers who died from hæmorrhage on the district were being given a plasma transfusion before the flying-squad arrived Surely the decision to transfuse must be taken by the man on the spot, whereas the decision to change to whole blood may properly be made in consultation with the obstetrician in charge of the flying-squad I imagine that similar procedures take place in hospital

This same report, suggests that if the flying-squad had been called earlier to cases of obstructed labour or malpresentation, before the practitioner had made abortive attempts to deal with the abnormality, some mothers might not have died

My object in writing to you, Sir, was to try and enlist your help in overcoming what can only be called lazy-mindedness in consultant obstetricians, who persist in the obviously false belief that there is some magical security in hospital buildings Everyone knows that most maternity hospitals in this country are converted poor-law institutes and that the astonishing results produced in hospitals during the past thirty years in lowering maternal mortality are due to the men and women who work in them Flying-squads provide a relatively cheap and easy method whereby these same men and women with their equipment can be transported to the mother's home

In this way, as far as I can see, only in this way, the interest and the enthusiasm of the general-practitioner obstetrician will be provoked He will learn to work as a member of a team and he will either subject himself to the disciplines of teamwork or will give up midwifery I repeat the only alternative is to deliver all women in hospital

Cambridge

C W WALKER

SIDE-EFFECTS OF LIBRIUM

SIR,—A new tranquillising drug, 7-chloro-2-methylamino-5-phenyl-3H-1, 4 benzodiazapine-4-oxide hydrochloride ('Librium'), is now available commercially It has been widely advertised in terms of its taming effect on wild animals and claims have been made that it is of special value in controlling phobic and obsessional symptoms in psychoneurosis although the published evidence for this is slight[2]

9 outpatients with phobic anxiety states and 6 with obsessional neuroses have been treated with this substance for three weeks The dosage given was 10 mg thrice daily for the first week and 25 mg thrice daily thereafter Only 3 of the 9 phobic patients and 1 of the 6 obsessional neurotics felt any subjective improvement.

Side-effects were seen in over half the patients 2 felt drowsy on the smaller dose, 5 on the larger 2 felt fatigued and apathetic, and dizziness and constipation were reported. 1 patient felt more energetic and 2 complained of severe irritability After taking the drug for a week a schoolteacher struck his wife for the first time in the twenty years of thei marriage Of the 15 patients, 3 had to stop work because of th side-effects and 2 others refused to continue taking the dru after two weeks

Although the number treated is small and the findings uncontrolled, the results are disappointing enough and the side effects sufficiently troublesome to deserve attention Othe side-effects reported in trials in the United States have include dissociative reactions, hyperactivity, and ataxia.[3]

We feel justified in suggesting that the drug should b used with circumspection and scepticism until the result of controlled trials are available

Southern General Hospital
Glasgow

I M INGRAM
GERALD C TIMBURY

MORE CHROMOSOME ANOMALIES

SIR,—In a leading article[4] you discussed the relation between the so-called sex-chromatin or Barr bodies and X chromosomes May I draw attention to some new facts and hypotheses that throw light on these problems?

Yerganian[5] recently found two types of X chromosomes in female Chinese hamsters (*Cricetulus griseus*), a predominant X_1 and a retarded X_2[6] The predominant X_1 has a secondary constriction in a heterochromatic arm with a small pericentric euchromatic segment The retarded X_2 has no secondary constriction and is strictly confined to the female Ohno et al's[7] observation of different heteropyknosis in the X chromosomes of the female rat, only one of which forms the Barr body, seems to indicate that the X_1 chromosome of the Chinese hamster with its secondary constriction is the sex-chromatin-forming chromosome, but only so in the presence of an X_2 chromosome This hypothesis implies a triheterosomic sex determination, normal females being X_1X_2 and normal males X_1Y

Earlier observations already revealed more complicated heterosomes in some mammals,[8] but Yerganian et al[6] now extend this hypothesis to most mammals and man They discuss whether X_1 chromosomes can become differentiated to X_2 chromosomes so that an X_1X_1 combination results from fertilisation or alternatively X_2 differentiates to X_1 in X_1Y combinations If Xs do not have the faculty to undergo this differentiation, what happens in the 50% of zygotes that are X_1X_1 or X_2Y? The authors are inclined to interpret X_1X_1 individuals as Turner's syndrome with 46 chromosomes and negative sex chromatin as observed by Ford et al[9] Turner's with 45 chromosomes and absence of Barr bodies would be X_1O The X_2Y combination would be a sex-chromatin negative individual with the testicular feminisation syndrome. Chromatin positive (X_1X_2Y) and negative (X_1X_1Y) Klinefelter's syndrome are both understandable by this hypothesis

In my opinion this hypothesis deserves further attention but fails to give a clear answer to the question of the often undesirable combinations as X_1X_1 and X_2Y in the event that X chromosomes do not have capacities for differentiation. Another hypothesis is based on the well-known fact that fertilisation in mammals and man takes place in the oocyte II stage of meiosis The second polar body is expelled after sperm entrance.[10] I suppose that when the X_1 sperm enters the oocyte II the second meiotic spindle is oriented so that the X_1 half of the female nucleus is expelled and when the Y sperm enters the X_2-half is expelled This implies that the oocyte II has a X_1X_2 constitution and undergoes postreduction so that in meiosis I one (or an uneven number of) chiasmas are formed between the centromeres and differential segments of the X chromosomal bivalent The anomalies just mentioned, then, are caused by non-disjunctions and anomalous orientation of the second meiotic spindle In my opinion this hypothesis deserves no complicated sex-linkage mechanism as Yerganian et al imply

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[1] Report on Confidential Inquiries into Maternal Deaths in England and Wales, 1955-57 H M Stationery Office, 1960

[2] Breitner, C *Dis Nerv Syst* 1960, 21 (suppl 3), 31

[3] Tobin, J M, Bird, I F, Boyle, D E *ibid* p 11

[4] *Lancet*, July 23, 1960, p 191

[5] Yerganian, G *Cytologia*, 1960, 24, 66

[6] Yerganian, G, et al (in the press)

[7] *Exp cell Res* 1959, 18, 415

[8] Beatty, R A *in* Sex Differentiation and Development London, 1960

[9] *Lancet*, 1959, i, 711

[10] Witschi, E Development of Vertebrates, p 43 Philadelphia, 1956.

Further data are needed to elucidate the sex-determining mechanism in man. Yerganian's theory and my additional hypothesis may, I hope, stimulate further research

Genetic Laboratory,
R.K. Universiteit,
Nijmegen, Netherlands
S J GEERTS

PERPHENAZINE IN HUNTINGTON'S CHOREA

SIR,—Various attempts have been made during recent years to modify the uncontrolled movements of Huntington's chorea The drugs used have been procaine amide,[1] reserpine,[2] and some of the phenothiazines (including chlorpromazine,[3] thiopropazate [' Dartalan '],[4] perphenazine [' Fentazin '],[5] and trifluoperazine [' Stelazine '][6]) On the whole those drugs with the greatest tendency to produce parkinsonism are most effective for treating hyperkinetic symptoms But one must remember that drugs such as perphenazine and trifluoperazine[7] are themselves liable to produce hyperkinesis

I have used perphenazine in two cases because of its close chemical resemblance to thiopropazate, and because the first case I treated developed a rash with thiopropazate but not with perphenazine Apart from this the results were equally good with either drug

CASE 1.—A widow, aged 43, was admitted to hospital in April, 1955 There was no family history of nervous or mental disease. Movements typical of Huntington's chorea had begun 2 years previously and had become worse during the past 12 months She could not manage to climb stairs, and she had often fallen off chairs, sustaining numerous injuries She also had headaches, depression, and insomnia, and she had lost weight.

The following drugs were given with little or no effect phenobarbitone gr 1/2 t.d.s., procaine amide tablets 0 5 g q.i.d., reserpine 1 mg t.d.s., benzhexol (' Artane ') up to 10 mg t.d.s., and meprobamate 400 mg t.d.s

In October, 1958, she was given thiopropazate 10 mg t.d.s., and the dose was gradually increased over 6 weeks to 30 mg t.d.s At this stage she was able to walk about without falling but some involuntary movements persisted when her attention was attracted. In February, 1959, a severe rash necessitated discontinuing this treatment, and she was given promethazine as tablets and ointment. The involuntary movements gradually returned, and the rash subsided.

Perphenazine was then given in doses of 8 mg t.d.s at first, and gradually worked up to 20 mg t.d.s She continued to take this dose until the end of October, and meanwhile the clinical improvement was the same as it had been with thiopropazate

At about this time trifluoperazine became available, and it was thought that the same effect might be obtained with smaller doses than those needed with perphenazine It was substituted without any intervening period, and the dose was raised gradually to 25 mg b.d. by the end of the year But both the staff and the relatives, who took her home on leave, agreed that she was not as well as she had been on either thiopropazate or perphenazine. She was accordingly given perphenazine again in January, 1960, and the dose was rapidly raised from 8 to 20 mg t.d.s She remained on this dose without ill effect until April, when she became unduly quiet and almost immobile. The perphenazine was therefore stopped until her " normal " choreiform movements returned. It was resumed 3 weeks later in a dose of 12 mg t.d.s and increased to 18 mg t.d.s in a week. She has taken this dose ever since and is leading a more active life than would otherwise have been possible She has slight movements, but can get up and down two flights of stone steps to the occupational therapy department Her speech is clear, but slow, and she takes an interest in her surroundings and relatives

CASE 2.—A Ukrainian man, aged 42, who had been living in lodgings but could not be managed, was admitted to hospital in July, 1960 He could only walk with difficulty, and choreiform movements were very marked, especially when he was in bed and awake His speech was indistinct.

Perphenazine was started in a dose of 8 mg t.d.s., gradually increased to 20 mg t.d.s within 3 weeks, and later reduced to 18 mg t.d.s because of a fall in blood-pressure. The improvement in speech and gait, and diminution of movement, was similar to that noted in case 1 The patient became easily managed, and helped on the ward. He is at present working in the light industrial centre at the hospital.

A colleague who had charge of a chronic sick ward also gave perphenazine, in doses of 10–16 mg t.d.s., to four very advanced bedridden cases with choreiform movements One became worse, and the others did not improve

The effects of perphenazine in the two cases of Huntington's chorea, however, seem to be sufficiently encouraging to warrant further study on a larger scale

My thanks are due to Dr Stanley Smith, medical superintendent, for permission to publish these cases, and for his cooperation which enabled me to treat case 2, also to Dr Douglas A Kent for his helpful advice and by treating the advanced cases

Lancaster Moor Hospital,
Lancaster
R. PAKENHAM-WALSH

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[1] Goldman D Amer J med Sci 1952 224 573
[2] Kempinsky, W H, Boniface W R, Morgan P P Busch A K Neurology 1960 10 38
[3] Vaughan, G F Leiberman D M Cook L C Lancet 1955 i, 1083
[4] Matthews, F P Amer J Psychiat 1958 114 1034
[5] Lanacha R Basen A Minerva Med 1958 49 suppl 39 p 1993
[6] Oliphant, J Evans, J L, Forrest A D J ment Sci 1960 443, 715
[7] Ross L Brit med J Aug. 13, 1960, p. 522.

NEPHROTOXICITY OF ACETYLSALICYLIC ACID

SIR,—The belief that long-term abuse of analgesics may cause chronic interstitial nephritis with renal failure[1 2] has been widely accepted. Usually in such cases the patient has taken mixed analgesics containing phenacetin, acetylsalicylic acid, acetanilide, or other drugs Of these, phenacetin has been suggested as the nephrotoxic agent

In short-term provocation experiments it was earlier shown that the urine-sediment count is increased during treatment with phenacetin, especially if phenacetin contaminated with acetic-4-chloranilide is used.[3] In order to elucidate whether the increase in the urine-sediment count is due to a specific nephrotoxic effect of phenacetin or is a non-specific feature, the provocation experiments have been extended to include provocation with acetylsalicylic acid, phenylbutazone, and acetanilide

AVERAGE INCREASE IN ERYTHROCYTE AND LEUCOCYTE COUNT IN 12-HOUR URINE DURING TREATMENT WITH DIFFERENT ANALGESICS

Drug	Dose (g.) daily	No. of patients	Increase (%) in	
			Erythrocytes	Leucocytes
Pure phenacetin	3	11	16	38
Phenacetin contaminated with acetic-4-chloranilide	3	16	95	41
Acetylsalicylic acid	4	15	253	203
Phenylbutazone	0 8	10	39	36
Acetanilide	0 75	11	10	43

The daily intake was determined in accordance with the dosage clinically used. The sediment-count was determined for four days during which no drugs were given and for five days during treatment. For each patient the percentage change was calculated. The average rise for the patients in different groups is shown in the accompanying table, where our earlier results with pure phenacetin and phenacetin contaminated with acetic-4-chloranilide are included for comparison.

Much to our surprise acetylsalicylic acid and not phenacetin seems to cause the highest degree of kidney irritation. For a definite evaluation of the relative toxicity of the drugs, comparative studies with all the drugs in the same person(s) are necessary Such experiments are going on at present

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[1] Spühler, O Zollinger, H U Helv med Acta 1950 17 564
[2] Spühler, O Zollinger, H U Z klin Med 1953 151, 1
[3] Harvald, B, Valdorf-Hansen, F, Nielsen, A Lancet, 1960, i, 303

There is not necessarily any correlation between the increase in urine-sediment count during these short-term provocation experiments and the ability of the drugs to cause chronic interstitial nephritis after several years' administration On the other hand these preliminary experiments call for caution in replacing phenacetin as an analgesic with acetylsalicylic acid, which has been the tendency in Scandinavia of late years

Department of Medicine C,
Bispebjerg Hospital,
Copenhagen,
Denmark.

B HARVALD
E CLAUSEN

SPIRITUAL HEALERS IN HOSPITALS

SIR,—*The Lancet* reaches me three months late but I hope that I can still join in the correspondence on this subject

I feel that if we admit to the public for one moment that we do not know all the answers, that there are medical problems beyond our ken (whatever our private reservations may be), we shall be shaking the very foundations of our art This is not to imply that spiritual healing, faith healing, psychotherapy (call it what you will) has no place in medicine On the contrary The point is that we ourselves, consciously or unconsciously, must rely to a tremendous extent on " spiritual healing ", and must jealously guard our own rights and duties in this respect The good general practitioner (whether he realises it or not) is invested with the powers of a tribal medicine man, and therein lies much of his strength The hospital, with its ritual and drama and hidden mysteries, undoubtedly also exerts a similar influence As long as the patient has unbounded faith in the system, and as long as every person coming in contact with him, from the chemist-shop assistant to the ward charlady, overtly or tacitly strengthens his faith in the system, then he will derive as much benefit from our administrations as he can from any other source Let us not deny the existence of this healing power—the charming away of warts is accepted fact, after all Let us realise that we ourselves must rely for a large measure of our successes, however much it may go contrary to our " scientific " pride, on this same source of healing, whatever it may be This is not simply a matter of assisting an " unqualified practitioner ", as though we were letting him prescribe, or give an anæsthetic It is far more serious than that because to admit even the possibility that a spiritual healer can do something that we cannot do is to detract automatically, and in like measure, from our own effectiveness

Noumea, New Caledonia.

W NORMAN-TAYLOR

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P P/1

SIR,—We appreciate the studies reported by Dr Varadi and Mr Elwis (Sept 17) but wish to point out a serious misconception in their assessment of our recent investigation (Aug 6) Our only object in this particular paper was to demonstrate that a reasonable hæmatological response could be obtained with very small doses of the B_{12}-peptide complex. We were not particularly concerned either with the optimum therapeutic dose or with the serum-vitamin-B_{12} levels

As these two problems have been raised by Dr Varadi and Mr Elwis, however, it would assist us in understanding their work if they could tell us whether or not the patients they describe are the same ten to which Dr Varadi refers in an earlier letter [1] If they are the same patients, then might we ask whether all ten cases ultimately received 20 µg a day of B_{12}-peptide as stated in the first communication, or did only one receive this amount, as stated in the second letter? Furthermore, the case which is reported to have relapsed on a dose of 100 µg a day presumably did so before the earlier communication, since all ten cases had apparently been reduced to a daily dose of 20 µg by that time If this is true, was there any particular reason for failing to mention this relapse in the earlier letter, or was this relapse merely " a decline of the serum-B_{12} level " [1] and not a deterioration in the blood-picture?

Finally, as, apparently, the behaviour of the serum-B_{12} levels—and not the hæmatological responses—appears to be the main reason why they regard the B_{12}-peptide complex as unsafe, perhaps they would tell us what interpretation they put on their serum-B_{12} results, and what exactly is the scientific basis for such interpretation, when applied to this particular form of oral therapy

St. Helens Hospital,
St Helens

F S MOONEY
J G HEATHCOTE.

ANÆSTHESIA FOR NEUROSURGERY

SIR,—As I have been almost exclusively concer with neurosurgical anæsthesia for about twelve ye your editorial of Sept 17 interested me considerab particularly your references to the use of artific respiration

Since 1953 I have used controlled respiration neurosurgery, employing a machine which produces " positive-negative " pressure cycle I have anæsthetis over 1000 cases in this way, the majority of them bei major craniotomies, and over the past three years this h included posterior-fossa explorations

There has arisen a disagreement between the sen neurosurgeons at Bristol and myself over the resu achieved, which must of course be taken into accou when considering the pros and cons of the techniq However, personal observation, and reassessment of m results, has convinced me of the considerable benef achievable by proper use of controlled respiration, a I believe that Dr Galloon will endorse this from his ow experience

I have only some small comments about your editori

During operations conducted under mechanical controll respiration, I have often observed rhythmic cyclical changes the physical state of the exposed brain, occurring at the sam rate as the rate of artificial ventilation

At a point corresponding with the subatmospheric pha of the respirator, at which the recorded intratracheal pressu was reduced to about 4 cm of water below the barometr pressure, cortical veins were seen to collapse, and to ref with blood as the pressure rose There is of course a time la or phase shift, produced by the resistance and reactance the venous system extending between thorax and peripher cortical veins Moreover, the brain itself may be seen to pulsat at the respiratory rate, and quite independently of the pulsation due to the cardiac cycle This cyclical fall in venous pressure if not watched and moderated, can result in the drawing of a into vessels

I have the greatest respect for Dr Hunter, but your editori suggests that he denies that a change in intracranial pressur can accompany and be produced by artificial respiration. I my experience, and the *experience of my* surgical colleagues considerable changes can be produced in this way

Dr Hunter would not disagree that inadequate ventilation and/or a raised mean respiratory pressure, can produce very quickly a considerable increase in cerebral congestion, as h must have had occasion to observe this

Additional observations of the pressure changes accompanying mechanical respiration were made in my cases, by observing the rise and fall of cerebrospinal fluid level in both lumbar and intraventricular drainage systems, the fluctuations in pressure with each cycle seldom exceed a few millimetres of water, but are readily visible

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[1] Varadi, S *Brit med J* 1959, ii, 756

The longer-term changes in C S F tension which accompanied changes in the mean respiratory pressure were also observed, and these could amount to several centimetres of water

In an individual case, whether the brain movements accompanying respiration, or the C S F pressure changes, are the most striking, depends on the degree of overriding congestion, or decompression, already present If the dura is widely opened, and the brain is relaxed, it can move freely, and will be seen to do so with respiration, whether artificial or natural If it is engorged, but the drained ventricle is not collapsed, or the dura is closed, or only slightly open (as round the margin of a small parietal meningioma, for example), the brain movements are restricted, but fluctuations in blood content in the venous tree are transferred to the C S F, and the fluctuations will be very clear

The displacement of C.S F occurs presumably in the same way as the displacement during a Queckenstedt test

The phenomena are not always observable, and they are masked effectively if congestion and tension are already high In my experience they may be seen in at least three-quarters of all " cold " frontal and parietal craniotomies anæsthetised in this way When present they are quite evident, and do not require the eye of faith!

Dr Galloon has, I believe, confirmed to his own satisfaction that intracranial tension can be controlled by the correct use of controlled respiration, though I have not heard from him personally A recent paper from Oxford would suggest that Mr Pennybacker is inclined to agree

It is of course true that the introduction, from the United States, of the use of intravenous urea has proved of very great value in the control and treatment of cerebral swelling due to trauma, whether surgical or otherwise There do seem to be two possible disadvantages to be considered when deciding treatment with urea solutions

One is its effect on the peripheral venous system one case of extensive necrosis has arisen in my experience, though not fortunately in one of my patients, and there have been several cases of thrombophlebitis The other is the possibility of reactionary œdema at a later stage

Controlled respiration is not capable of reducing disastrous congestion, as is urea, once it has occurred, but it does seem to control its development during surgery, and in cases which are not seriously compressed preoperatively, and in which induction has not produced congestion, it maintains a relaxed brain, with freedom from venous congestion and oozing, without apparently any risk of subsequent reactionary œdema The most effective control of cerebral œdema seems to be anticipatory It is far more effective to act early, and hence to avoid being faced with an emergency, and the use of controlled respiration seems to give this early action in many cases, though it has been my practice to give hypertonic sucrose at induction to all cases where the intracranial tension is known to be raised, or there is papillœdema of a high order

Cases of frontal craniotomy for chiasmal and pituitary exploration do not show the orbital œdema in the postoperative period which was previously believed to be inseparable from frontal craniotomy

The major source of doubt as to the effectiveness of the method probably lies with the surgeon, not the anæsthetist. Such has certainly been my experience

Whether or not traumatic œdema develops either operatively or postoperatively depends to a large extent upon the detailed surgical technique, as well as upon the pathological changes In neurosurgery, no two cases are truly alike, and it seems that no two neurosurgeons wish to follow the same detailed technique Meticulous gentleness is a variable quality in the best of us, and yet in removing a tumour, the superfluous destruction of a draining vein may change the whole picture, and the whole prognosis A relaxed brain, with a relatively bloodless field, changes quite quickly to a state of severe congestion (" acute cerebral œdema ") without any assistance from the anæsthetist, who may now find his careful attempts to provide safe and easy operating conditions nullified!

The state of the brain is so dependent upon the factors of surgery, anæsthetics, and pathology that objective assessment of the value of any method can be difficult, without prolonged experience and the ability to learn from it

The observations outlined here were reported by me to the Society of British Neurological Surgeons in November, 1956 The technique of anæsthesia was described then, and also in a letter to the *British Journal of Anæsthesia* in November, 1957

Bristol. PETER L F MORTIMER

THE FEMALE PROSTATE

SIR,—Mr Thomas Moore[1] has excellently discussed the problem of lower urinary obstruction in the female I think he is also to be congratulated for his initiative and courage in stating " It is unfortunately still traditional for urinary symptoms in the female to lead to a gynæcological consultation " In Israel, too, dysuric females are often treated by gynæcologists and other doctors not specially trained in urology

Antibiotics may temporarily ameliorate certain symptoms, but may also mask certain lesions and lead to irreversible renal damage

Admittedly transurethral resection of the bladder neck in properly selected cases will give excellent results in both men and women with lower urinary obstruction But the resectionists' main concern is to avoid injury to the external sphincter In the male this sphincter is protected by the verumontanum, which serves as a landmark In the female the external sphincter is an ill-defined structure and there are no such landmarks Transurethral resection in the female is a rather delicate procedure in which an extra bite too far distally may transform obstruction into incontinence.

It seems to me that conservative treatment including persistent urethral dilatations should perhaps be tried first, reserving transurethral or open bladder-neck resection for cases in which it fails In 26 female patients who have come under my care operation (transurethral resection) has been needed in only 3

I agree entirely with Mr Moore that bladder-neck obstruction in women is not as uncommon as it is believed to be I feel that its frequency depends on the care with which it is sought A thorough urological examination, including voiding cystography, may reveal not only unsuspected obstruction of the bladder outlet but also its disabling sequelæ

Tel Aviv HERZL KOOK

ENDEMIC CRETINISM AND DEAF-MUTISM

SIR,—I have been waiting for an opening such as that provided by your leader of July 23, and I thank you for having provided it Among other questions raised by your thoughts is the question of the genesis of endemic cretinism and deaf-mutism Although I have nowhere come across a plausible explanation of the widely disparate frequencies with which deaf-mutism accompanies endemic goitre in different regions, there seems to be an explanation of these divagations in certain data collected by D Danielopolu and his collaborators in Rumania

I have them in book form (*Les Thyroïdies Endémiques et Sporadiques* published in Paris undated by Masson) but the book refers to previous publication in numbers 1 and 3 of the *Bulletin de l'Académie de Médecine de Roumanie* for 1937 On p 18 of Danielopolu's book, he defines what he means by *sourds muets* in the book by classifying their condition as *Surdi-mutité thyroidienne* under *Affections paragoitreuses* which is the fourth listing under *Thyroidies* The data which I should like to present are scattered from pages 50 to 63, and are those relating deaf mutism as just defined to economic status (see accompanying table) By economic status, I mean what

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[1] *Lancet*, 1960, i, 1305

GOITRE AND DEAF-MUTISM IN RUMANIA

Area	Approximate total population	No of subjects examined	No of goitres found	No of deaf mutes with an economic status of		
				Good	Average	Poor
Moldavitza valley	2000	1621	921	0 (208)*	0 (220)	9 (191)
Vatra-Moldavitza commune	1400	1381	523	0 (78)	0 (116)	2 (371)
Frumosuol commune	1500	1238	603	0 (39)	0 (63)	7 (151)
Vama commune	3000	2331	1087	1 (116)	0 (116)	16 (797)

* Figure in parentheses is number of uncomplicated goitres (*goitres normothyroidiens*) found in each group

Danielopolu calls *l'état matériel et l'alimentation quantitative* this is obviously closely connected with nutritional status

These data suggest strongly that deaf-mutism accompanies endemic goitre when the goitre is associated with poor nutritional status This suggestion is given further weight by Greenwald's observation [1] that endemic goitre seems to be accompanied by a high incidence of deaf-mutism in certain parts of South America and Europe, but not in the United States of America or Canada

Whippany,
New Jersey

MARSHALL E DEUTSCH

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[1] *J A M A Arch Otolaryng* 1959, 70, 511

Obituary

FRED THOMPSON BOWERBANK

K B E , M D Edin , F R C P E , F R A C P

Major-General Sir Fred Bowerbank, consulting cardiologist to Wellington Hospital and director-general of the New Zealand Army and Air medical services during the late war, died on Aug 25

He was born in 1880 at Penrith in Cumberland and educated at Edinburgh University, graduating M B in 1901 Soon afterwards he settled in New Zealand and, after a period in general practice, specialised in cardiology In the 1914–18 war he served with distinction with the New Zealand Expeditionary Force in Europe He remained in the Territorial Force and became D M S (Army and Air) for New Zealand On the outbreak of the war in 1939 he was made D G M S and remained head of the medical services until he retired in 1947 He was a fellow of the Edinburgh and Australasian Colleges of Physicians He was appointed O B E in 1917 and promoted K B E in 1946 He was also a grand officer of the Order of Orange-Nassau

A colleague writes

"Bowerbank was a man of wide interests and, outside his professional life, was a leader in such societies as Toc H, Crippled Children, and the Red Cross He had a distinguished personal appearance and was a man of great charm and had a host of friends He was one of the best known and most influential medical men in New Zealand over the past forty years"

Sir Fred Bowerbank married in 1907 Miss Muriel Pick, who survives him

HERBERT LEVY

M D Berne, M R C P

Dr Herbert Levy, senior hospital medical officer at Bethnal Green Hospital, died at his home in London on Sept 6, at the age of 56

He studied medicine in Berlin and Berne and graduated M D at the University of Berne in 1931 After holding hospital appointments in Germany, including a clinical assistantship with Prof P R Richter at the Hospital in Friedrichshain, Berlin, Dr Levy came to Britain as a refugee He took the Scottish triple qualification in 1935, and for a time he practised in Streatham At the beginning of the war he joined the London County Council hospital service and became assistant medical officer at Lambeth Hospital Later he joined the staff of the Bethnal Green Hospital He took the M R C P in 1945

A colleague writes

"Dr Levy was a true physician with a wide knowledge of Anglo-American and European writings on clinical medicine A fine diagnostician, with a rare discerning mind, he rose to the challenge of a difficult and unusual case, but his first consideration was always the patient and not the case He had many friends, not only among his colleagues and patients, but also in the worlds of art and literature He especially loved France and her art and literature Though he was aware of the seriousness of his condition for many years, he never let this interfere with his work, his devotion to his friends and their problems, and his zest for life"

Dr Levy leaves a wife and a young son

MELANIE KLEIN

Mrs Melanie Klein, who died in London on Sept 22 at the age of 78, was an original and creative psychoanalyst, who developed a technique of play-analysis for the treatment and study of small children

She was born in 1882 in Vienna, of Jewish parents Her youthful ambition was to be a doctor but an early marriage and family duties intervened Later her interest in the workings of the mind, particularly in children, drew her to the then new study of psychoanalysis, and she trained as an analyst under Ferenczi and Abraham She acknowledged the contribution each made to her development, but it was from Abraham that she received most insight and stimulus toward her original work

Child analysis was in its early stages in Berlin in 1921 when she began to develop her technique for the psychoanalysis of young children She came to England in 1926 to continue her work here at Ernest Jones' invitation Her published work included *The Psycho-Analysis of Children* (1932), *Envy and Gratitude* (1957), and *The Narrative of a Child Analysis* (in the press)

S I writes

"Melanie Klein saw that the play of even very small children reveals the content of their unconscious minds in essentially the same way that Freud had seen that verbal 'free association' revealed the hidden processes of the adult mind She also found it possible to relieve anxiety, even in children of only 2–3 years old, by putting into words for them what she saw of their unconscious fantasy life, showing that Freud's discovery of the therapeutic effect of interpretation can be directly applied to children Her technique of play-analysis has proved invaluable as a method of therapy and research Serious psychological disturbances, including psychotic illness, in children became accessible to treatment

"She worked out the details of early infantile methods of dealing with anxiety caused by powerful and conflicting impulses of love and hatred and saw that they were an extension of Freud's dynamic concept of the unconscious into the earliest stages of human life She studied the ways in which the loving and creative aspects of human personality can be overwhelmed, inhibited, or distorted by aggressive impulses, in children and adults Her recognition that very early infantile stages of emotional development can continue to exist within the adult made possible greater understanding of the origin of psychotic illnesses and their relationship to more normal states of mind. With this knowledge came improved skill in the psychoanalytic treatment of serious personality disorders and psychoses in adults In addition the influence of her work has been felt in the handling of mentally ill patients, the care of babies and young children, and in the management of schoolchildren as in the less obviously related fields of human creative thought and expression. Her great intellectual vigour, clarity, and coverage persisted throughout her life, and she was able to see patients and write until a few weeks before her death.

"Many people reacted to her work with fear, disgust, and hostile criticism. They were provoked particularly by the details of aggressive fantasies in very young children and by the idea of their persistence in adults It was one of the tragedies in the fruitful life of this indomitable Freudian that the opposition was so bitter at times But her work had a profound influence on the British Psycho-Analytic Society and on an increasing number of psychoanalytic groups She was also able to establish a small but vigorous and original group of colleagues She may have sometimes been irked or wearied by opposition but was never surprised by it, for she shared with Freud a deep understanding of the fear of the unknown and in particular a respect for the human being's fear of the unconscious forces within his mind. She combined in her small frame feminine charm and interests with unusual intellectual gifts which she had the strength of purpose to use. The importance of her scientific discoveries may be partly beyond general comprehension at the moment But history places people in their right perspective, and though Melanie Klein was accorded relatively little credit in her life time, the importance of her work will be appreciated realistically in the future.

"What can be the effect of one woman courageous enough to look into the human mind in its developmental stages and see its struggles with aggression? There is the encouragement we gain from the example of someone engaged throughout a long life in the unremitting search for scientific truth, however frightening or unpalatable. Also there is the hope that increased understanding of their unconscious impulses will eventually enable human beings to preserve from their own destructiveness all that they value most."

Sir HAROLD GILLIES

R. E R. writes

"In the last five years of his life, Sir Harold Gillies visited India a number of times and helped to establish plastic surgery units as well as visiting centres of medical teaching and research. Though he could not give much time he had done a great deal of operating and teaching in the units and regarded them as his own creations and their staff as his pupils"

A memorial service to Sir Ernest Rock Carling will be held at St. Margaret's, Westminster, at NOON on Monday, Oct 3

Appointments

Birmingham School Health Service

TOMSON, R. C. F, M.B. Edin. school M.O
TYLER, JANET B, M.B. Lond. school M.O.
WILLIAMS, DAVID, M.B. N.U.I., D.A. school M.O

Colonial Appointments

BOWMAN, R. K. M.R.C.S., D.P.H. chief M.O., Gilbert and Ellice Islands.
CHUI WAN CHEONG, J P A F, M.B., D.OBST M.O., Mauritius.
CLYDE, D F, L.M.S. Nova Scotia specialist malariologist, Tanganyika.
FOWLER, A. F, M.R.C.S., D T.M. & H., D.P.H. principal M.O. Uganda.
HEARD, R. G. P, M.B. Dubl., D T.M. & H. senior M.O (clinical), Tanganyika.
HEYWOOD B E C, M.R.C.S., D.P.H., D.I.H. deputy chief M.O., Uganda.
OAKEY, J S., M.B. Sydney, D T.M. & H., D.P.H. senior M.O., Tanganyika.
RUNCIMAN, CHARLES M.B. W'srand, D.P.H., D T.M. & H., D.I.H. senior M.O. (administrative), Tanganyika.
SWEENEY T K., M.B. N.U.I., D T.M. & H., T.D.D. senior M.O. Tanganyika.
WONG, HOK NIN, M.B. Hong Kong principal medical and health officer, Hong Kong.

Notes and News

RHODESIA AND NYASALAND TEACHING HOSPITAL AND MEDICAL SCHOOL

REAFFIRMING in Salisbury on Sept. 23 his Government's decision to establish a multiracial teaching hospital and medical school attached to the University College of Rhodesia and Nyasaland,[1] the Federal Prime Minister, Sir Roy Welensky, said

"Doctors are in short supply throughout the world and in addition existing medical schools are becoming overcrowded with fewer and fewer places available to students from abroad. In clear terms, the position today is that we can no longer continue to expect other countries to train our medical students nor expect other countries to supply the bulk of our demand for medical, nursing, and allied, professional people. The time has come to provide for our own needs.

"After most careful consideration, the Rhodesia Medical School Planning Committee have concluded that the advantages of having a medical faculty and teaching hospital in close proximity are so great that despite some increased capital cost for a hospital of this nature the building of a teaching hospital is justified. Therefore I am able to announce tonight that the Federal Government have accepted the obligation to build, equip, and staff a teaching hospital of some 350 beds on a twenty-five acre site adjacent to the University College at Salisbury

"It is estimated that buildings will cost about £1 4 million and that the annual operating cost including capital redemption will be in the nature of £0·5 million. My Government accepts this considerable responsibility in order to hasten and assure the progress of medical and health services of the Federation. The establishment of a medical school—a million pound project with an annual recurring charge of some £235,000 only slightly offset by revenue from fee-paying students—may seem a formidable task and indeed it is, but I am happy to be able to acknowledge considerable support already promised to the University Medical School, particularly from the Nuffield Foundation itself which has made an offer of no less than a quarter of a million pounds.

"At the same time, the University of Birmingham has offered to sponsor medical degrees and I believe I speak for the whole Federation when I say how deeply appreciative we are of this action, which will enable our young medical students to receive degrees which will rank among the best, and to be taught by men and women of the highest quality and qualifications"

OUTBREAK OF TUBERCULOSIS IN AN IMMUNISED COMMUNITY

IN one of the northernmost counties of Sweden, Warfvinge[2] says, at least 90% of the children born since 1940 have had B.C.G vaccination and about 10% of them have been revaccinated at school age, because the tuberculin reaction had faded out. In these circumstances the population, numbering about 5000, might well expect not to be troubled by tuberculosis Indeed in 1955–56 a survey by mass radiography was fully reassuring But in the spring and early autumn of 1958 a crop of pleurisies in 9 youngsters started a hunt for suspects This extended gradually from members of the patients' family to fellow workers, shops, dairies, and other sources of food, yet the culprit could not be found As the number of new cases rose, mass radiography was again undertaken, being applied wholesale in November, 1958 Even so the mystery might have remained unsolved had not a youth of 19, who had eluded radiography, volunteered for clinical examination because of an obstinate cough. His sputum teemed with tubercle bacilli, and both lungs were the seat of cavernous tuberculosis A devotee of dancing, he had also engaged in kindred activities calculated to promote a liberal exchange of germs By last April the number of people he had infected was 27—of whom 20 had pleurisy and all but 2 were between sixteen and twenty-three years of age. All 27 have fared well, and it is perhaps significant that miliary and meningeal tuberculosis have been conspicuous by their absence 17 of the 20 patients with pleurisy had been vaccinated with B.C.G once or oftener

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[1] See *Lancet*, July 16, 1960 p 139

[2] Warfvinge, L. *Kvartalsskrift Svenska Nationalföreningen Mot Hjärt-Och Lungsjukdomar* 1960, 55, no 2.

University of London

The following degrees have been awarded

M D—J A M Ager, George Belyavin, David Burman
M S—I F K Muir

Royal College of Surgeons of England

On Thursday, Oct 20, Prof J F Nuboer will give a Moynihan lecture He will speak on recurrent peptic ulcer after gastrectomy On Thursday, Oct 27, Dr Cuthbert Dukes will give a Thomas Vicary lecture His subject will be genetics in relation to surgery Both lectures will be given at 5 P M at the college, Lincoln's Inn Fields, London, W C 2

Royal College of Surgeons of Edinburgh

On Wednesday, Oct 19, at 3 30 P M , at the college, Mr Eric Samuel will give a lecture on mechanical syndromes following partial gastrectomy

Royal College of Obstetricians and Gynæcologists

At a meeting of council on Sept 24, with Sir Andrew Claye, the president, in the chair, the following were admitted to the membership

Augustus Amartei Armar, Christian Bam, Dhirendra Nath Banerjee, Sreemanta Kumar Banerjee, N M D Blyth, Pauline M Bousquet, A H Bradfield, G F Bradfield, I T Brake, Tancred Busuttil, I E Cary, K L Collins, Joan M Curtis, L S Deane, Marie T D'Netto, R F Heys, Ma Hla-Kyi, Florence P Isaiah, W I H Johnston, J B Jones, Karapati Kanakadurgamba, William Kelso, J F Kemp, J F Leeton, J L Marcus, J M Mistry, W M Moore, E D Morris, Barun Kumar Mukherji, Olusola Adewole Ojo, P R B Pedlow, W S E Perera, Walter Pollard, Doreen Rothman, Anjul Kumar Sinha, Sarel Johannes Smal, A M Smith, H J Solomon, Bruce Sutherland, T E Torbet, A R Trist, W L Whitehouse

St. Mary's Hospital, London

Dr G B Mitchell-Heggs has been appointed dean of the Medical School in succession to Mr A G Cross

College of General Practitioners

On Sunday, Nov 20, at 10 A M , at the Wellcome Building, Euston Road, London, N W 1, the college will hold a symposium on mental health and the family doctor In the morning there will be a discussion on emotional disorders in general practice (Dr E C Hamlyn, Dr Michael Balint, and Dr David Stafford-Clark), and in the afternoon on the psychoses in general practice (Dr J R Rees, Dr John Horder, and Dr Russell Barton) Further particulars may be had from the secretary of the college, 41, Cadogan Gardens, Sloane Square, London, S W 3

Ophthalmological Society of the United Kingdom

The annual congress of this society will be held from April 13 to 15 at 1, Wimpole Street, London, W 1, when Mr F W Law will give his presidential address Miss Ida Mann has chosen for the subject of her Bowman lecture Climates, Cultures, and Eye Diseases The programme will also include a discussion on neovascularisation in ocular disease (Prof Norman Ashton and Mr Redmond Smith) and a symposium on the late complications of aphakia (Mr A J B Goldsmith and Mr J R Hudson) Further particulars may be had from the society, 47, Lincoln's Inn Fields, W C 2

Sir Andrew Claye is visiting Nigeria at the invitation of the Federal Government in connection with the independence celebrations

On Friday, Oct 14, at 3 P M , at the University of Leeds, Sir Robert Aitken will give the inaugural lecture to the faculty of medicine His subject will be Medicine Today and Tomorrow

Dr G M Carstairs is to give a lecture at the Marlborough Day Hospital, 38, Marlborough Place, St John's Wood, London, N W 8, on Monday, Oct 3, at 8 15 P M He is to speak on recent trends in American Psychiatry

At a meeting of the Cambridge Medical Society on Wednesday, Oct 19, at 8 30 P M , at Owen Webb House, 1, Gresham Road, Cambridge, Dr L S Penrose will speak on mongolism.

The second edition of the *International Catalogue of Mental Health Films* has been published by the World Federation for Mental Health The editor is Dr T L Pilkington and copies (21*s* each) may be obtained from the Federation, 19, Manchester Street, London, W 1

At a meeting of the Medical Electronics Discussion Group c Friday, Oct 7, at 6 P M , at the Institution of Electrical Engineer Savoy Place, London, W C 2, the subject for discussion will b nerve-endings The opening speakers will be Dr O C J Lippol and Dr D R. Wilkie

The autumn dinner of the Wessex Rahere Club will take plac at the Grand Spa Hotel, Bristol, on Saturday, Oct 29, under th chairmanship of Dr Russell Grant Membership of the club is ope to all Barts men practising in the West Country The hon secretar is Mr A Daunt Bateman, 11, The Circus, Bath

The Medical Research Council have reprinted from their annua report for 1958–59 reviews of research on selected medical and bio logical subjects which they think will interest scientific and lay a well as medical readers Copies of *Current Medical Research* (3*s* 6*d* may be had from H M Stationery Office

The National Committee on Maternal Health, Inc (2, East 103r Street, New York 29, N Y), have published a *Selected Bibliograph of Contraception 1940–1960* The editor is Dr Christopher Tietze Free copies will be supplied to schools, libraries, and governmenta and non-profit organisations

Semipermanent exhibitions will be held during the autumn at th Institute of Dermatology, Lisle Street, London, W C 2 The first from Oct 3 to 7, will be by Dr Henry Haber on normal skin

The Hospitals Symphony Orchestra, which meets on Mondays a 7 30 P M in St Thomas House, Lambeth Palace Road, London, S E 1, has vacancies in all string sections and in some of the wind and brass sections Further particulars may be had from Miss M A Whipp, South Western Hospital, Landor Road, S W 9

Births, Marriages, Deaths

DEATH

MACINTYRE —On Sept 23, Eneas John MacIntyre, M D Glasg , formerly M O H for Sutton and Cheam and Banstead, at the age of 62 years

Diary of the Week

OCT 2 TO 8

Monday, 3rd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 P M *United Services* Air Commodore G H Morley Role of Plastic Surgery in the Royal Air Force

Tuesday, 4th

ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P M Dr Wilson, F INST P Nuclear Physics
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr Ian McCaul Involuntary Movement

Wednesday, 5th

ROYAL SOCIETY OF MEDICINE
5 15 P M *History of Medicine* Prof K J Franklin Charles I and Harvey
8 P M *Surgery* Prof C Lambert Rogers Surgical Problems of the Cervical Spine
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
2 P M Prof G M Bull Place of Chemical Pathology in Medicine
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr Henry Haber Histology of Normal Skin
INSTITUTE OF DISEASES OF THE CHEST, Brompton Hospital, S W 3
5 P M Dr J R Bignall Problems of Lung Cancer
UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Miss U M Lister Endometriosis
6 P M Sir Andrew Claye Dyspareunia

Thursday, 6th

ROYAL SOCIETY OF MEDICINE
8 P M *Neurology* Dr W H McMenemey Immunity Mechanisms in Neurological Disease (Presidential address)
WEST LONDON MEDICO-CHIRURGICAL SOCIETY
8 P M (Rembrandt Hotel, Thurloe Place, S W 7) Mr Harvey Jackson Pathways to the Brain (Presidential address)

Friday, 7th

ROYAL SOCIETY OF MEDICINE
10 30 A M Dr R S Allison Dr J H D Millar, Dr Henry Miller, Prof C E Lumsden, Dr E J Field, Dr J B Finean, Prof G Payling Wright, Prof R H S Thompson, Prof S Refsum (Oslo), Prof G I Scott, Dr Rowland Farrell Disseminated Sclerosis and Allied Conditions (All-day symposium)
POSTGRADUATE MEDICAL SCHOOL
10 A.M Prof L N Pyrah Aspects of Renal Calculi
1 P M Prof G M Bull Regulation of Water and Salt Excretion

Saturday, 8th

BRITISH ASSOCIATION OF PHYSICAL MEDICINE
10 15 A.M (Royal Sussex County Hospital, Brighton) Provincial autumn meeting

The Lancet · Saturday 8 October 1960

ESSENTIAL HYPERTENSION

HÆMODYNAMIC OBSERVATIONS WITH A BEARING ON ITS PATHOGENESIS *

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PRAGUE-KRČ, CZECHOSLOVAKIA

ESSENTIAL hypertension is generally attributed to an increase in peripheral vascular resistance, with a normal cardiac output (Bolomey et al 1949, Werko and Lagerlof 1949, Pickering 1955) Since no morphological vascular changes are detectable, at any rate at its onset, the causes of the increased vascular resistance are thought to be either nervous or humoral, with a slight bias towards the latter possibility According to the nervous concept (Lang 1950, Mjasnikov 1954), the fault lies in an imbalance of the central nervous system (neurosis), but this does not explain why the regulation of blood-pressure is alone disturbed The humoral concept, which relates hypertension to the pressor substances originating in ischæmic sclerotic kidneys, has been weakened by the demonstration that in the early stages of the disease the kidneys are anatomically intact (Talbott et al 1943, Goldring and Chasis 1944, Smith 1948) Though other humoral agents have been invoked—e g , noradrenaline (von Euler 1952) and pherentasine (Schroeder 1951)—convincing evidence of their role is still lacking

Hines (1940) showed that some normotensive subjects, when their hands are immersed in cold water for a minute, respond by a steeper rise of blood-pressure than the majority of healthy people, and he found that such hyper-reactors were more apt to develop hypertension later In a study with the " dynamic cold pressor test ", in which not only the amount of the rise but also the whole course of the reaction is noted, we found that the response was exaggerated and protracted in 21 out of 39 normotensive subjects (54%) with a family history of hypertension but in only 7 out of 62 (11%) without such a history (Brod et al 1954a) Comparable differences between normotensives and hypertensives were observed in the pressor response to mental stress (Wolf and Wolff 1951, Brod et al 1959)

Since an abnormal course of the pressor response to simple environmental stimuli is seen most often in people who will later have permanent hypertension, we need to know what is the relation between these abnormal blood-pressure rises and permanent hypertension. One possibility is that the protracted responses are repeated so frequently that they fuse But this explanation implies that the hæmodynamic changes of the acute pressor reaction are the same as those of essential hypertension Actually the pressure response to emotion is associated with a rise of cardiac output (Stead et al. 1954), whereas the cardiac output of the hypertensive is usually normal, and at first sight this seems to be a major obstacle to the hypothesis But, by ballistocardiography, Wolf and Wolff (1951) found that, whereas in most normotensives a rise in blood-pressure during emotional stress is due to an increase in cardiac output (C O), in most hypertensives it is due to an increase in total peripheral vascular resistance (T P R.) Because of the unreliability of ballistocardiography for quantitative assessment of cardiac output and therefore for estimation of changes in T P R , this work was repeated by Hejl (1957) with the dye-dilution method He confirmed that, after pressor stimuli, blood-pressure might rise through one of three mechanisms (1) cardiac output increases while T P R remains unaltered or falls (type I), (2) T P R. increases while cardiac output remains unaltered or falls (type II), (3) cardiac output and T P R. increase simultaneously (type III) Whereas the cold stimulus most often evokes responses of types II and III, both in normotensives and in hypertensives, emotional stress (see below) evokes type I in 75% of normotensives but type II or III in 80% of hypertensives

These results suggested that there may be two or three different patterns of hæmodynamic behaviour, depending both on the nature of the stimulus and on the characteristics of the person investigated The apparent resemblance between the general hæmodynamic pattern of essential hypertension and a type-II response to the acute pressor test called for further research—bearing in mind the fact that T P R is only an integration of the regional vascular changes which may differ individually in magnitude and even in direction

In essential hypertension the increase in T P R. is thought to be due to a more or less parallel increase of the resistances in all the important vascular areas of the body This view, however, is based on the finding of a normal blood-flow through the whole arm (Prinzmetal and Wilson 1936) or through the skin (Pickering 1936) in hypertensive subjects A possible fallacy is that the levels of blood-flow through muscle and skin may change in opposite directions, and that a change of blood-flow in muscle may thus escape detection when blood-flow in the whole extremity, or in the skin only, is determined

Except that there is vasoconstriction in the kidneys (Wolf and Wolff 1951, Brod et al. 1954b) and skin (Brod et al 1954a), relatively little is known about the regional hæmodynamic changes underlying acute pressor responses in man

For deeper insight into the relation between the abnormal pressor responses of still-normotensive subjects and the permanent elevation of blood-pressure of hypertensives, we need therefore, to re-examine the " resting " hæmodynamics of essential hypertension and compare them with the hæmodynamics of acute pressor responses This has been attempted, for both conditions, by *simultaneous* observations of the resistance changes in the most important hæmodynamic areas of the body

Method of Investigation

The method used had to be " physiological ", and to cause as little trauma as possible, so that the results should not be affected by extraneous factors Briefly, it consisted in the following procedures (Brod et al 1959)

Thin polyethylene tubes were introduced percutaneously into the right brachial artery and the right antecubital vein by the Holmgren (1956) modification of the Seldinger (1953) technique Both tubes were attached to threeway stopcocks

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* Based on a lecture given at the University of Bristol on June 21, 1957, and the Burns lecture to the Royal Faculty of Physicians and Surgeons of Glasgow on Feb 26, 1958

A microinfusion of inulin and *p*-aminohippurate (P A H) was given through the venous tube at a rate of 0 3 ml per min The other tap of the venous stopcock was used for injections of congo red or rose-Bengal which were employed as indicators for dye-dilution estimation of cardiac output The arterial tubing was connected, by one tap of the threeway stopcock, with a capacitance manometer for direct blood-pressure estimation, while the other tap was connected with a sampling apparatus (2-second intervals) Any of these procedures could be started simply by turning the stopcocks, without the slightest disturbance and even without the knowledge of the person under investigation, whose whole forearm was hidden from his sight by a curtain

The disappearance curve of rose-Bengal was used in later investigations as an indicator of splanchnic blood-flow, 80% of this dye being removed from the blood by the liver (Hoenig and Schuck 1956) Skin blood-flow was assessed on the right forearm either qualitatively by thermometry or quantitatively by the Hensel-Bender (1956) thermocapsule Muscle blood-flow was calculated from the difference between blood-flow through the left forearm—estimated by occlusion plethysmography (Barcroft and Swan 1953)—and blood-flow through a corresponding area of the skin This method afforded simultaneous information about the changes of blood-pressure (mean blood-pressure was estimated planimetrically) and cardiac output, from which the changes in T P R could be calculated), and changes in flow and vascular resistance in the kidneys, in the splanchnic area (if rose-Bengal was used as dye-indicator), and in skin and muscle

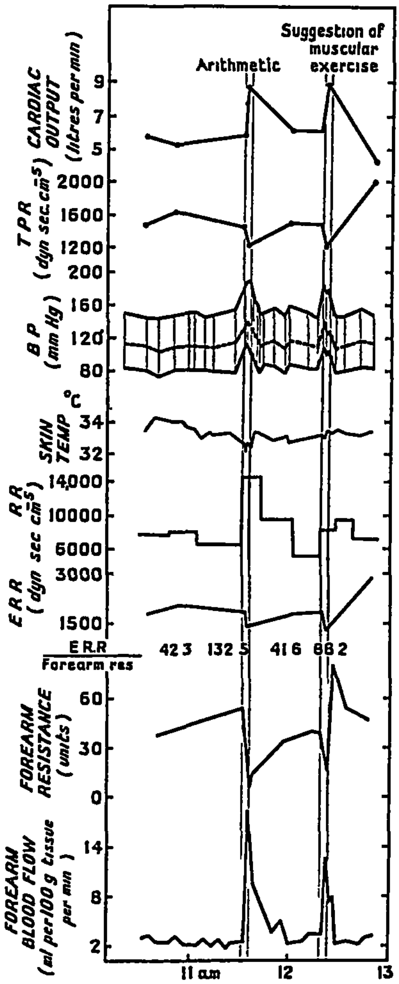

Fig 1—Hæmodynamic changes during an acute blood-pressure rise produced by stressful mental arithmetic and by a verbal suggestion of strenuous muscular exercise in a normotensive subject

During the verbal suggestion of exercise the subject was asked to close his eyes and to imagine that he was riding a bicycle uphill for 10-minutes Further details in text

C O = cardiac output T P R = total peripheral vascular resistance B P = blood-pressure, (dotted line = mean blood-pressure) R R = renal vascular resistance E R R = extrarenal vascular resistance ($\frac{1}{TPR} = \frac{1}{R.R.} + \frac{1}{E.R.R}$) Forearm-res = forearm vascular resistance

Pressor Reaction in the Normotensives

The course of investigation, and a typical result in one of our nine normotensive subjects, is shown in fig 1 After a control period of 1 hour, during which blood-pressure was stabilised at about 140/80 mm Hg, the subject was asked to start with the number 1194 and subtract 17 consecutively every 2 seconds This stressful stimulus lasted 4 minutes, during which time both the systolic and diastolic pressures rose by 25 mm Hg With this increase in blood-pressure, the cardiac output rose from 5 5 to 9 0 litres (+47%), while the T P R decreased by some 250 dynes sec cm^{-5}* (−13%) Thus, the general hæmodynamic response in this subject was of type I At the same time there was vasoconstriction in the kidneys, evidenced by a rise of renal resistance from 6500 to 14,700 dynes A drop in the forearm skin temperature while the blood-pressure was rising indicated vasoconstriction in this vascular area, but a rise in blood-flow through the forearm from 2 5 to 17 5 ml per 100 ml. forearm per min indicated vasodilation in the muscle Extrarenal vascular resistance (calculated from the difference between the reciprocal values of total peripheral vascular resistance [T P R] and renal resistance) also diminished but to a much smaller extent than the part of it contributed by muscle This is also evident in the rise of the extrarenal-resistance/muscle-resistance ratio from 42 to 132 From these results it is clear that some other part of the extrarenal vascular area does not take part in the vasodilation or may even contract After cessation of the stimulus the blood-pressure and the other investigated hæmodynamic functions returned promptly to control levels

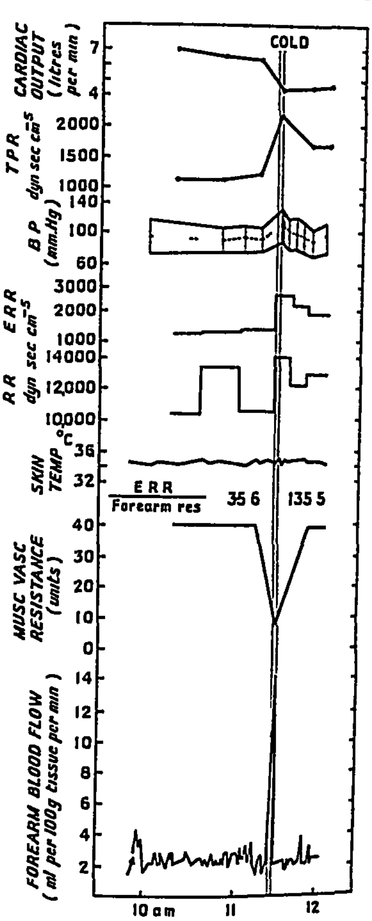

Fig 2—Hæmodynamic changes during a blood-pressure rise induced by immersion of right leg in cold water (4°C) for 2 minutes in a normotensive subject.

A type-II hæmodynamic response in a normotensive subject following immersion of one leg in cold water (4°C) for 2 minutes is shown in fig 2 The blood-pressure rise was obviously produced by a rise of T P R, while cardiac output decreased slightly However, the detailed hæmodynamic changes were analogous in quality, and of similar duration, to those of the previous subject there was vasoconstriction in the kidneys and skin and vasodilatation in muscle, while a rise of extrarenal resistance indicated vasoconstriction in some important part of the extrarenal vascular bed other than muscle (the extrarenal-resistance/muscle-resistance ratio was raised) This suggested splanchnic vasoconstriction, which was more directly supported by the slower decline of the rose-Bengal disappearance curve after the same pressor stimuli in later experiments Further, in two patients with colostomy the same pressor stimuli were found to reduce the temperature of the exposed intestinal mucosa

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* Hereafter abbreviated as " dynes "

Fig 3 summarises the hæmodynamic effects of the pressor stimuli studied (mental stress and cold) in our normotensives The subdivision is into three arbitrary groups corresponding to the three types of hæmodynamic response mentioned above The heavy lines indicate the direction and magnitude of the average change of each of the functions investigated In all three groups the pressor stimulus evidently induced vasoconstriction in skin and kidneys, with vasodilatation in muscle The changes in extrarenal vascular resistance differed in the three groups, but we have to remember that the extrarenal area includes, besides muscle (where vasodilatation takes place), the splanchnic area The rise in the extrarenal-resistance/muscle-resistance ratio, together with the more direct evidence already mentioned, suggests splanchnic vasoconstriction in all three groups Thus the responses in the various vascular areas are of the same kind in all three groups, but in degree they are differently distributed In responses of type I (the usual reaction to mental stress) vasodilatation in muscle prevails over vasoconstriction in the kidneys, splanchnic area, skin, and possibly other areas, and consequently T P R tends to fall In responses of types II and III (the usual reactions to cold) the vasoconstriction prevails over muscular vasodilatation, and T P R rises (In fig 3, type III is represented by only one subject.) Evidently the degree of visceral vasoconstriction increases with the strength of the stimulus Cardiac output rises where T P R falls, but it also rises where, because of perfect balance between the vasoconstrictor and vasodilator components of the response, T P R does not change This suggests that the higher cardiac output is not the result of a lower T P R but is an integral part of the hæmodynamic response to pressor stimuli It has been observed even where, because vasoconstriction slightly prevailed over vasodilatation, T P R. was a little raised (type III) Only when T P R rose by 20% or more did cardiac output fall Such a fall was seen in subjects who had perfectly normal hearts capable of overcoming far more than the 20% increase in T P R , so the idea that the fall in cardiac output is caused by failure of the myocardium can be dismissed Similar observations have been made by others studying changes of cardiac output as related to the changes of T P R (Warren and Stead 1947, Aviado et al 1950, Fejfar and Brod 1954, Sarnoff 1958) and can be explained partly by reflex actions

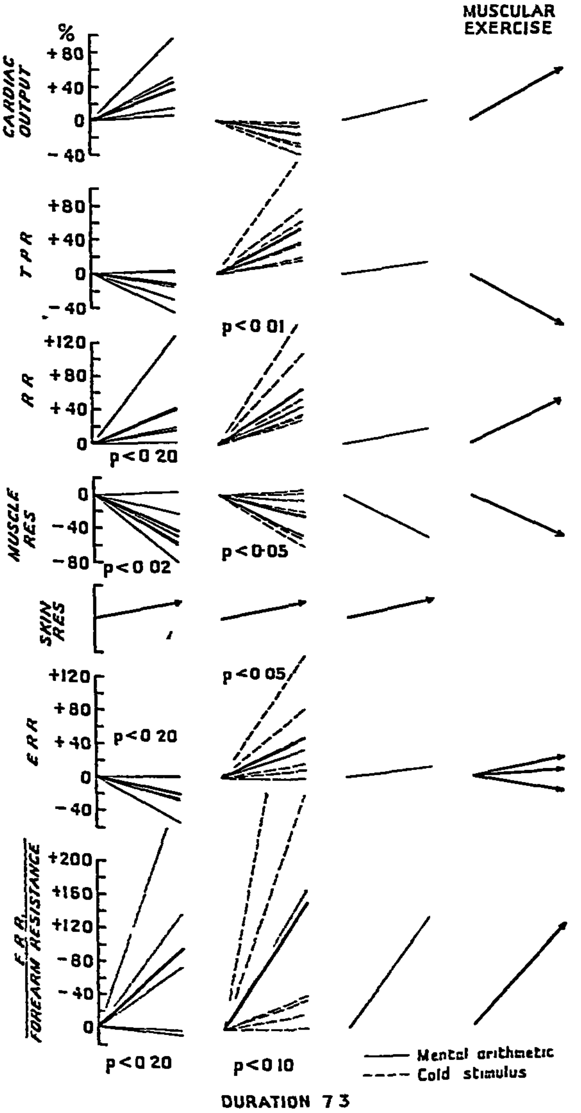

Fig 3—Summary of hæmodynamic changes induced by pressor stimuli in all normotensive subjects.

Skin resistances were studied in a separate investigation, so only the resulting qualitative change in the whole group is indicated by arrow On the right, the qualitative changes of regional vascular resistances during muscular exercise (as known from the literature and our own investigation) are indicated by arrows

The statistical significance was evaluated by Student's t test Owing to the small number of subjects and the scatter, P did not reach statistical significance in some of the subgroups However, if calculated for all subjects without subdivision into subgroups, R.R and E R.R. forearm-resistance changed significantly during pressor stimuli The trend of change is the same and is clearly visible in all the subgroups

Under our experimental conditions the response to the pressor test in our normotensive subjects disappeared in an average of 7 3 minutes after cessation of the stimulus

Mechanism and Biological Significance of the Pressor Reactions

The efferent vasoconstrictor pathway of this reaction lies, unquestionably, in the sympathetic nervous system it is possible to prevent the emotional vasoconstriction in the kidneys with dibenamine (Brod et al 1954) But the vasodilator mechanism in muscle is less certain Emotional vasodilatation can be induced in a sympathectomised forearm (Barcroft et al 1958), and this, together with the fact that vasodilatation lessens or disappears after adrenalectomy, points to its being mediated by circulating adrenaline However, atropinisation of the forearm usually diminishes vasodilatation (Hejl and Brod 1959, Blair et al 1959), and this suggests that at least part of the vasodilatation is mediated by cholinergic fibres

A hæmodynamic response consisting of an increase of cardiac output, vasoconstriction in the kidneys, splanchnic area, and skin,† and vasodilatation in muscle, recalls the changes of severe muscular exercise In some subjects, however, we were able to induce them merely by a verbal suggestion of strenuous effort—e g, riding a bicycle uphill Fig 1 shows that this suggestion had the same hæmodynamic consequences as the mental arithmetic an hour before

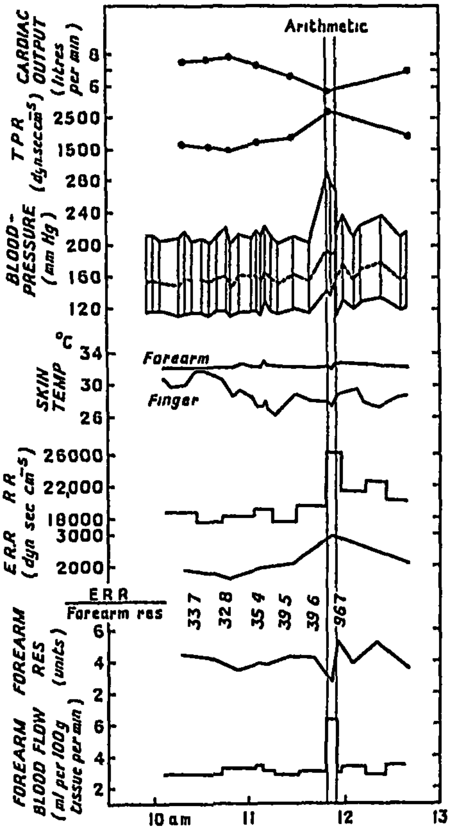

Fig 4—Hæmodynamic changes during blood-pressure rise induced by stressful mental arithmetic in a hypertensive patient

Analogous changes in the regional distribution of the blood—vasoconstriction in the skin and viscera, vasodilatation in muscle—were induced by Eliasson et al (1951), in anæsthetised cats and dogs, by electrical stimulation of a large area of the hypothalamus In unanæsthetised cats, in which electrodes had been implanted into certain areas of the hypothalamus, electrical stimulation resulted in a typical rage reaction, in addition to the hæmodynamic changes (Abrahams and Hilton 1958) Stimulation with a current of lower intensity induced, besides the hæmodynamic changes, movements of head, eyes, and ears, recalling the " orientation reflex " of Pavlov (1927)—the search for danger and threat Such an orientation reflex is always associated with a transient rise of blood-pressure, lasting some 15–20 seconds, and a fleeting vasoconstriction in the skin but not in the muscles of the limbs (Madlafousek 1957) Here again the rise in blood-pressure is obviously connected with a shift of blood to muscle

This striking similarity between the circulatory responses to strenuous muscular action, to its verbal suggestion, to emotional stress, to rage, and to an orientation reflex suggests a common denominator This, I submit, is to be found in strenuous muscular exercise

What is the actual significance of emotional stress? It is a psychological consequence of danger—of a threat Self-preservation may require violent muscular action an animal or a child will usually defend itself against a real or imagined danger by fight or flight In adult human beings, we may suppose, the vegetative component of this reaction is preserved, even when social restraints prevent any visible action Investigations of the orientation reflex suggest that this reaction, which prepares the organism for action, is activated in each of us many times a day but is promptly inhibited when it is obviously inappropriate Judging by experiments on animals, it is integrated at a hypothalamic level

Pressor Reaction in Hypertensives

A response mental stress, typical of our twelve hypertensives, is shown in fig 4 The 4 minutes' mental arithmetic raised both systolic and diastolic blood-pressures by almost 50 mm Hg, and 40 minutes later the pressure was still above its initial level The rise was due to an increase in T P R from 1900 to 2800 dynes, while cardiac output showed a small decrease. Renal resistance rose from 18,000 to 26,000 dynes, and after 30 minutes it was still above its initial level A slight fall in skin temperature despite the raised blood-pressure indicated vasoconstriction in the skin The rise in extrarenal vascular resistance was again suggestive of splanchnic vasoconstriction, in view of the increased extrarenal-resistance/muscle-resistance ratio and the fact that muscle blood-flow more than doubled while muscle resistance fell

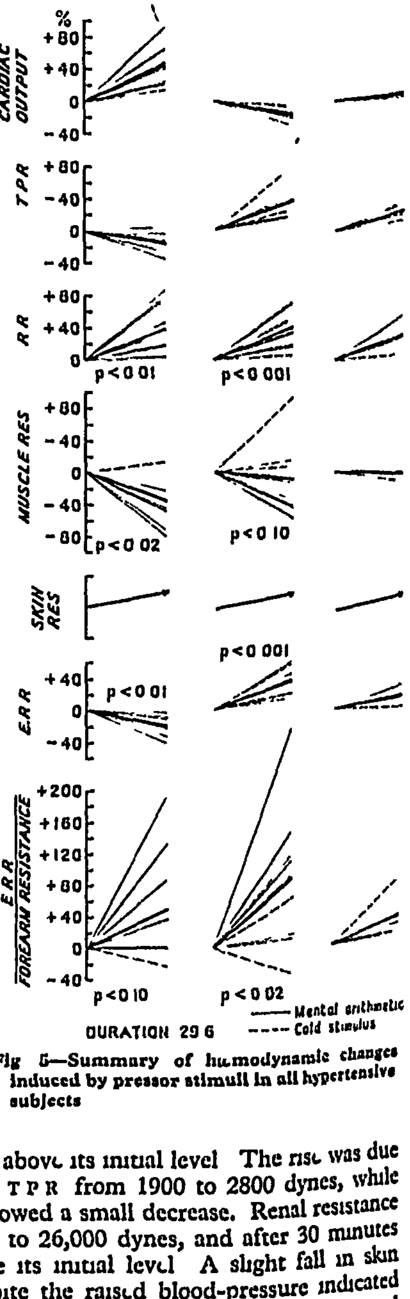

Fig 5—Summary of hæmodynamic changes induced by pressor stimuli in all hypertensive subjects

Fig 5 summarises our data for hypertensives—most of them in the early stage of the disease and none showing signs of heart-failure (The subdivision into three groups is the same as in fig 3) In *quality* their response does not differ appreciably from that of normotensives it consists in visceral and cutaneous vasoconstriction with muscular vasodilatation, and the behaviour of the cardiac output depends, as in normotensives, on the changes in T P R But the reaction lasts much longer In those tests in which the baseline was eventually regained, its average duration was 29 minutes, and in three the blood-pressure was still raised when the test ended some 30–45 minutes after cessation of the stimulus. Thus the course of the reaction differs substantially in normotensive and hypertensive subjects.

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† According to our experience there is always cutaneous vasoconstriction at the start of muscular exercise With continuing exercise, especially if severe, this gives way to vasodilatation, perhaps associated with thermoregulation (Fencl et al 1959)

The response differs also in *quantity* (fig 6). Renal vasoconstriction is greater in the hypertensives, while muscular vasodilatation (decrease in muscular vascular resistance) appears to be less—though this difference was not statistically significant. The hypertensive obviously responds to pressor stimuli by an exaggerated visceral vasoconstriction which is not balanced by a corresponding muscular vasodilatation. The fact that vasoconstriction prevails explains why, in hypertensives, responses of types II and III are commoner than responses of type I (Hejl 1957), but, as there is no basic qualitative difference between the reaction patterns, they cannot be sharply distinguished. Thus the claims of Wolf and Wolff (1951) that normotensives raise their blood-pressure by increasing cardiac output, whereas hypertensives do it by a rise of T.P.R., were only partly substantiated by our work.

The average systolic/diastolic rise in blood-pressure following immersion of one leg into cold water was 11·2/11·0 mm Hg compared with 18·8/15·5 in hypertensives (Brod et al 1954). This points to an abnormal relation, in hypertensives, between cardiac output and T.P.R. In the type-I response cardiac output increases more than can be accounted for by the fall in T.P.R. In types II and III the rise in T.P.R. does not inhibit the rise in cardiac output as efficiently as it does in normal subjects.

Further, Malkova (1952) has drawn attention to the clinically well-known fact that in hypertensives a rise in blood-pressure can be induced with much smaller stimuli than are needed in normotensives.

Resting Hæmodynamics in Hypertensives

The regional distribution of vascular resistance while at rest has been investigated in 31 normal subjects and in 55 patients with essential hypertension (mostly in its early stages). Fig 7 shows that, compared with the normals (set at 100%), the hypertensives have higher resistances in the renal, splanchnic, and cutaneous areas, while their muscle resistance is lower. Thus in resting hypertensives blood is shifted from the viscera and skin to muscle, just as it is in normotensives under emotional stress or (at first) during severe muscular exertion.

A similar conclusion about the character of the hæmodynamic change underlying essential hypertension was reached in a previous study (Brod and Fencl 1957) on the diurnal hæmodynamic rhythm in normotensives and hypertensives. In normotensives the mean blood-pressure changes very little between night and day: whenever cardiac output rises, the increased blood-supply is accommodated by an expanding vascular bed (not only in muscle but also in the kidneys and possibly in other tissues) and normal pressure is quickly restored on cessation of exercise or of emotional stress. (In kidneys and skin a period of hyperæmia often follows vasoconstriction [Brod et al 1954a and b].) In hypertensives, on the other hand, the mean blood-pressure tends to rise in the morning. The vascular bed in the kidneys and some extrarenal area—possibly splanchnic—constricts, and T.P.R. therefore increases. If this increase is large, the rise of cardiac output usually accompanying transition from night inactivity to day activity is replaced by a fall.

Thus the hæmodynamics of an acute pressor reaction in normotensives resemble in all respects the hæmodynamics of hypertensives at rest.

Pathogenesis of Essential Hypertension

All the above experimental data depend, of course, on the accuracy of the methods used, particularly of the method for estimation of skin blood-flow, which is crucial to the assessment of muscle blood-flow. The

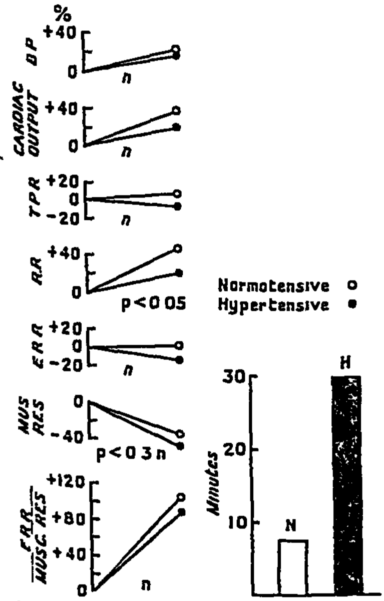

Fig. 6.—Comparison of magnitude and duration of the hæmodynamic changes produced by mental stress (mental arithmetic) in normotensives (N) and hypertensives (H).

There are no differences between normotensives and hypertensives in the behaviour of C.O., T.P.R., and E.R.R. The difference in R.R. reached statistical significance, that in muscle resistance indicated a trend towards less vasodilation in hypertensives, without attaining statistical significance. The columns on the right indicate differences in duration of the reaction.

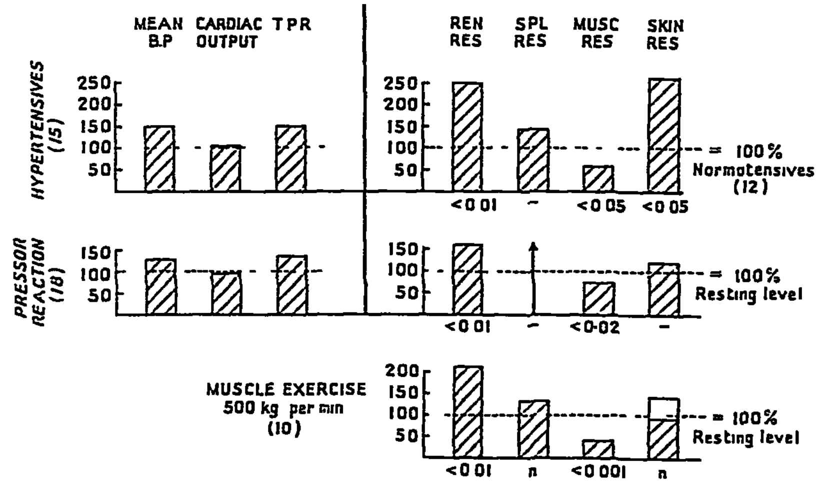

Fig 7.—Comparison of the hæmodynamics of hypertensives at rest with type-II pressor reaction in normotensives and with the response to strenuous exercise.

The dotted line, indicates the basis for comparison (resting hæmodynamics of healthy normotensives in line 1 and control resting values of the investigated subjects in lines 2 and 3).

In the studies of pressor reaction changes of total forearm resistance are indicated. As the skin resistance has an increasing trend, the true decrease of vascular resistance in muscles is greater than indicated. The arrow in place of splanchnic resistance indicates the direction of its change assessed from changes of E.R.R.

This figure was constructed from the data of the first investigated series of 12 normotensives and 15 hypertensives. The data for the larger series fit in well with those for the earlier part of the investigation.

method used in the above work is, however, probably the best available at present If correct, then the rise of blood-pressure in essential hypertension, at any rate in the early stages, can accordingly be explained by the hypertensive being in a state of more or less permanent readiness for muscular action This explanation differs from previous ones in that essential hypertension is *not regarded as something newly acquired but simply* as the result of disturbed regulation of one of the fundamental hæmodynamic responses of the organism On this basis we need not be surprised that the distinction between normal and hypertensive states is not sharp or that in early hypertension no anatomical changes are encountered anywhere in the body

To discover why regulation of this fundamental reaction is disturbed, much further work will have to be done When studying pressor responses repeatedly in the same person, we (Brod et al 1954c) were struck by the way their course sometimes changed when the tests were carried out in adverse circumstances for example, the response might be exaggerated or protracted if the subject was troubled by the illness of a relative or by a recent quarrel with a colleague In the causation of essential hypertension, accumulation of adverse environmental factors—stress and traumatic events—has often been indicted (Kammerer and Molitor 1917, Schulze and Schwab 1936, Ehrstrom 1945, Lang 1950, Mjasnikov 1954, Brod et al 1954c), and we may reasonably suppose that if these factors are perpetually provoking hæmodynamic reactions, the normalising restorative mechanisms will eventually weaken, and the circulatory system will become continuously keyed to action The fact that this is no more than an exaggeration of an ordinary physiological response explains why only an increase in blood-pressure is induced and not some other functional disturbance Differences in the capacity of the regulatory mechanisms to stand up to wear and tear would explain the familial prevalence of the disease

Where, exactly, the regulatory mechanisms are disturbed we do not yet know Several clues (electro-encephalographic and pharmacological, for instance) point to the central nervous system, but, before reaching any conclusions we shall have to exclude possible changes in the effector organ—i e, in the response of the smooth muscle of the blood-vessels When this question is settled, when the role of pressor substances of renal and other origin is clarified, and when we gain more understanding of the metabolic aspects of hypertension—then only can we hope for a solution of this part of our problem

Summary

During acute blood-pressure rises following emotional or cold stimuli, blood is shifted from the kidneys, splanchnic area, and skin to muscle The changes of *the total peripheral vascular resistance* depend on the balance of the vasoconstrictor (viscera, skin) and vasodilator (muscle) components of this reaction A rise of cardiac output is an integral part of the pressor reaction, and is superseded by a fall only in those instances where total peripheral vascular resistance rose markedly through a preponderance of visceral vasoconstriction over muscle vasodilatation

The changes in regional hæmodynamics are analogous to those accompanying severe muscular exercise They can also be produced by verbal suggestion of muscular exercise It is suggested that preparation for severe muscular exercise is the common denominator of this hæmodynamic response

In essential hypertension the resting regional hæmodynamics are analogous to those of the acute pressor reaction with a preponderance of visceral (and skin) vasoconstrictor components over muscular vasodilatation It is suggested that essential hypertension is due to a *disturbed regulation of this basic hæmodynamic reaction* preparing the organism for muscular action

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CELL-DIVISION IN CARCINOMA DURING RADIOTHERAPY

A CRITERION OF RESPONSE TO TREATMENT

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ABNORMAL mitosis is a striking feature of growing tissues that have received irradiation, and many of the cells succumb when they attempt to divide In the course of cytological studies on biopsy material from cases of cervical cancer undergoing radiotherapy, I have found that one week after the first radium treatment mitoses are often numerous, but that many are grossly abnormal Furthermore, the absence in most cases of the later stages of division (anaphases and telophases) indicates that most if not all of the cells entering mitosis at this time are incapable of completing division In this paper, I wish to show that the presence of normal anaphases and telophases one week after the beginning of treatment is usually associated with poor local response to treatment.

Materials and Methods

All patients received an initial radium treatment by a modified Stockholm technique (one 50 mg intrauterine tube and two 30 or 20 mg intravaginal ovoids, in situ for 22 hours), followed in most cases by two further radium insertions (on day 7, and either day 14 or day 21), in a few cases the initial radium treatment was followed by external irradiation from a ^{60}Co source or a 4 MeV linear accelerator to the whole of the pelvis Biopsy material was obtained under anæsthesia, in most cases immediately before the second radium insertion No effort was made to cut deeply into the tissues, usually, superficial tissue from the growing edge was removed by punch-biopsy forceps

After overnight fixation in 1/3 acetic alcohol, a piece of tissue about 2 mm in diameter was placed on a slide, and covered by a drop of acetic orcein (G T Gurr, Ltd) It was broken up by tapping with a flat-ended metal rod, the material being spread out to correspond to the area of the cover-slip ($1^1/_2 \times {}^7/_8$ in.) which was then applied The preparation was sealed with a mixture of equal parts paraffin wax and Canada balsam, applied with a hot wire Some disintegration of the tissue was inevitable during the preparation, but large clumps of cells remained, together with a number of free cells, or nuclei more or less devoid of cytoplasm No difficulty was experienced in distinguishing tumour cells from normal cells in mitosis, the latter being found in fibrous or necrotic areas and generally being smaller Two slides were routinely scanned, using a 10× objective, clumps of tumour cells were examined for the presence of dividing cells with a 40× objective

Results

One week after the first treatment, the changes known to occur after irradiation were seen in varying degree—namely, cellular enlargement, increase in necrosis, decrease in normal mitoses, and the appearance of abnormal mitoses The frequency of mitoses varied widely in different cases, and bore no obvious relation to the response to treatment Abnormal metaphases having scattered or degenerating chromosomes or chromosome-fragments were seen in nearly every specimen, irrespective of the response However, the presence of normal anaphases and telophases was clearly correlated with a poor response to radiotherapy, since, in 11 out of 13 cases in which they were found, either the tumour failed to regress or there was an early local recurrence (within eight months) (table I) Brief details of these cases are given in table II

TABLE I—RELATION BETWEEN PRESENCE OF NORMAL ANAPHASES AND TELOPHASES ONE WEEK AFTER FIRST TREATMENT AND SUBSEQUENT LOCAL RECURRENCE

—	No local recurrence (no of cases)	Local recurrence (no of cases)	Total
Normal anaphases or telophases absent	106 (*91%*)	11 (9%)	117
Normal anaphases and telophases present	2 (*15%*)	11 (*85%*)	13

The minimum period of follow-up of the cases in this study was nine months, the mean being 24 2 months Local recurrences developed in 11 cases in which normal anaphases and telophases were absent (table I), in only 4 of these cases, however, was the recurrence manifest within eight months of treatment A correct forecast of the early outcome of treatment —i e , up to eight months—was thus provided in 124 of the 130 cases (95%)

When normal anaphases and telophases were present never less than 6, and often more, were found on two slides routinely examined Abnormal anaphases and telophases (with chromosome fragments or bridges) were usually present as well, but were seldom found when the corresponding normal figures were absent

Discussion

Ideally, it should be possible to determine the radiosensitivity of a tumour before treatment Failing this, it would be of value to be able to predict the ultimate response from the nature of the changes that take place in the tumour soon after the beginning of treatment No morphological or cytochemical feature of the untreated tumour has yet been found that provides a sure guide to the radiosensitivity of carcinoma of the cervix, although certain features of the normal epithelial cells, desquamated from mucosa in the neighbourhood of the tumour, may indicate whether it is likely to respond to irradiation (Graham and Graham 1956) The histological appearances of squamous-cell tumours are of little value in predicting the outcome of treatment (Warren et al 1939, Merrill 1958) However, Glücksmann and Cherry (1956) have found that adenoacanthomata of the cervix frequently respond poorly

TABLE II

Case no	Age (yr)	Stage	Histological diagnosis	Treatment *	Subsequent course
1	50	IV	Adenoacanthoma (undiff)	One Stk. followed by D.X.R. to whole pelvis (5000r)	Failed to regress
2	40	I	Adenoacanthoma (undiff)	3 Stk.+D.X.R. to parametria	3 mos cervix still firm, 8 mos extensive local recurrence
3	59	II	Adenoacanthoma (undiff)	3 Stk.+D X.R. to parametria	At end of treatment, tumour was little changed $2^1/_2$ mos later, active tumour at primary site
4	52	II	Squamous cell (mod well-diff)	3 Stk.—D.X.R. to parametria	3 mos local recurrence proved by biopsy
5	42	I	Squamous cell (undiff)	3 Stk.	7 mos local recurrence, proved by biopsy
6	38	I	Squamous cell (mod well-diff)	3 Stk.	3 mos local recurrence, confirmed at operation
7	34	III	Adenoacanthoma (largely undiff)	3 Stk.	Poor immediate response. Positive biopsy from cervix at 3 mos
8	43	IV	Squamous cell (undiff)	1 Stk. followed by irradiation (4 MeV linear accelerator) to pelvis	$3^1/_2$ mos positive biopsy from ulcer on cervix
9	46	I	Squamous cell (mod well-diff with anaplastic areas)	3 Stk.	$2^1/_2$ mos Wertheim s hysterectomy (poorly diff squamous cell carcinoma in post. fornix and adjacent cervix)
10	39	I	Squamous cell (undiff)	3 Stk.	4 mos local recurrence, confirmed at operation
11	34	III	Squamous cell (undiff)	1 Stk. followed by irradiation (4 MeV linear accelerator) to whole pelvis	4 mos died, active tumour present in cervix

* Stk.=Stockholm radium insertion D.X.R.=deep X ray Undiff =undifferentiated. Well-diff.=well-differentiated

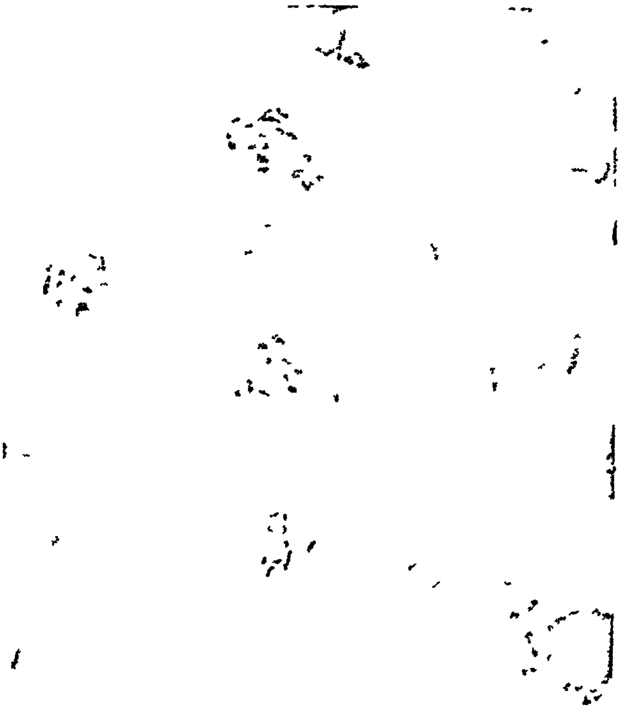

Fig 1—Clump of tumour cells with several abnormal divisions (×560)

Several studies have been made of the changes seen in serial biopsies during radiotherapy for carcinoma of the cervix Besides throwing light on the sequence of events in tumours following irradiation, these studies have in some instances provided the basis for methods of predicting the effectiveness of treatment In a review of currently available "radiosensitivity tests", Merrill (1958) has indicated the limitations that may restrict their usefulness, for instance, biopsies may not be representative of the tumour as a whole, and owing to the presence of a strong subjective factor in the assessment of some criteria, the results obtained by one group of workers may not be repeatable by a different group Many workers found that a decrease in normal mitoses and increase in abnormal mitoses followed irradiation (Dustin 1927, and Meigs Parker 1930, Frola 1933, Warren et al 1939, Glücksmann and Way 1948, Kistner and Hertig 1951 A critical study of mitotic abnormalities is probably not possible in the sectional material used by these workers

The presence of normal anaphases and telophases appears to be a clear indication that response to therapy has been slight, since an important effect of radiation on living cells is the destruction of their proliferative capacity (Gray 1959), Normal anaphases or telophases were never found in biopsies taken on day 14 or day 21, even when they had been present on day 7 It may be, therefore, that the time at which normal divisions are found in resistant tumours is rather critical It would be worth determining whether in resistant tumours at other sites, treated by different radiotherapeutic techniques, normal cell division is also present at about the stage when a third of the treatment has been given

The amount of necrosis in a specimen was not clearly correlated with the response, although resistant tumours on the whole showed less necrosis than those that responded This is a feature that may be expected to vary in different parts of the same tumour In case 11, there was much necrotic tissue in the specimen nevertheless, in several of the relatively small clumps of tumour cells present, normal anaphases or telophases were found Similarly, the total number of cells in mitosis was not obviously correlated with the radiosensitivity, nor was the degree of enlargement of the interphase nuclei Although normal mitoses were present in resistant cases, abnormal forms usually still predominated For instance, in case 1, which clinically showed a very poor response to treatment, a count of 1000 tumour cells revealed 13 prophases, 36 metaphases, 6 anaphases, and 8 telophases clearly in this tumour there were numerous metaphases, many of which were seen to be abnormal In spite of this cytological evidence of radiation damage, the presence of the later division stages, most of which were normal, indicated that some of the tumour cells were able to divide normally Nuclear enlargement is hard to evaluate Microspectrophotometric estimations of D N A content of a small series of cervical carcinomata undergoing radiotherapy have, however, helped to throw some light on the

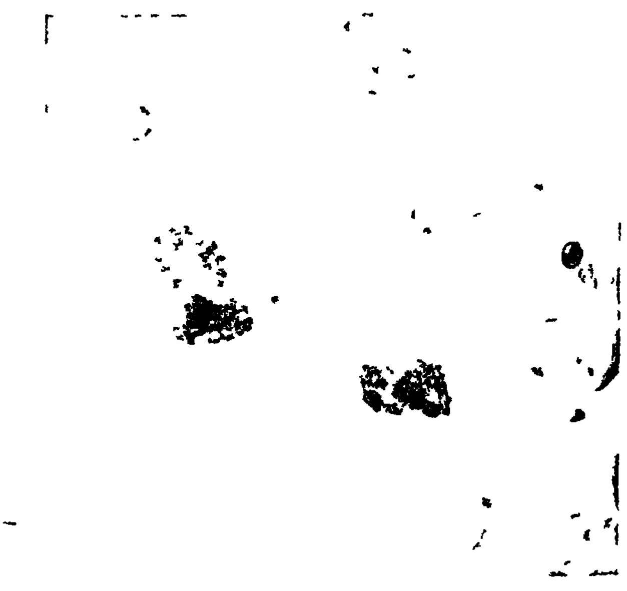

Fig 2—Normal telophase (left) and anaphase, case 8 (×750)

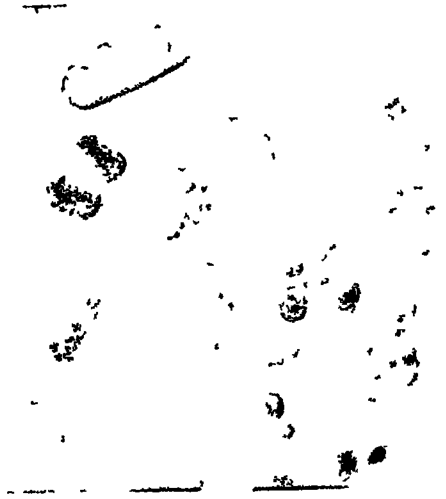

Fig 3—Normal anaphase, case 11 (×750)

(Acetic orcein "squash" preparations of biopsy material obtained one week after the first radium insertion Fig 1 from a tumour that showed a good local response, figs 2 and 3 from tumours that recurred locally) nuclear changes that occur during treatment (Richards and Atkin 1959) In case 1, a patient with an adenoacanthoma of the cervix, they provide a clue to the presence of many abnormal metaphases and to some nuclear enlargement, although a few of the cells were apparently able to divide normally the D N.A. data suggest that there was a selection of radioresistant elements having a triploid D N A content from what was originally a mixed population

The findings reported here have been related to the response of the primary tumour only Although it may not indicate those cases that will fail through inability of the treatment to deal with extension of the tumour, the presence of normal anaphases and telophases may nevertheless provide an early indication of a poor local response to treatment

Summary

Using a " squash " technique, biopsy material from 130 cases of carcinoma of the cervix, obtained one week after the first radium treatment, has been examined for the presence of cells in mitosis

Prophases and metaphases were usually present but normal anaphases and telophases were noted in only 10% of the cases

The presence of normal anaphases and telophases correlated well with local recurrence of the tumour within eight months of treatment (in 11 out of 13 cases)

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ANTICOAGULANT TREATMENT OF OBLITERATIVE PULMONARY HYPERTENSION

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Repeated minute pulmonary embolism is a recognised cause of " idiopathic " or " primary " pulmonary hypertension Such small pulmonary emboli are often symptomless, and these repeated silent emboli may insidiously obliterate the pulmonary vascular bed and thus build up the pulmonary arteriolar resistance to produce irreversible right ventricular failure

In the absence of overt signs of pulmonary embolism or infarction, treatment with anticoagulant drugs is often not considered Their use, however, may be followed by a gratifying result, as is illustrated by the following case-report of a young woman who presented with obliterative pulmonary hypertension of unknown cause (" idiopathic pulmonary hypertension ")

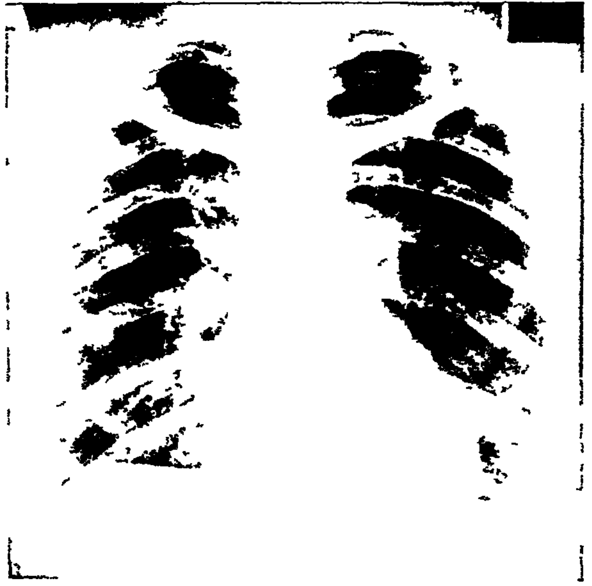

Fig 1—Chest X-ray before treatment.

The pulmonary artery is enlarged, the peripheral vessels are unremarkable

Case-report

A married woman, aged 32, was delivered of her first child by forceps after a long labour in February, 1957 The puerperium was normal in every respect, and in particular there was no history of venous thrombosis, leg pain, chest pain, hæmoptysis, or any abnormal vaginal discharge Six months later she began to have symptoms, becoming breathless for the first time whilst pushing the pram up the hill outside her home. During the next five months she had two syncopal attacks, each precipitated by exertion.

When admitted to Hammersmith Hospital on May 5, 1958, she had the clinical features of pulmonary hypertension. There was no cyanosis or clubbing An " a " wave 3 cm. above the sternal angle could be seen in the venous pulse, the arterial pulse was normal There was slight right ventricular hypertrophy, and on auscultation the second sound in the pulmonary area was narrowly split, with the pulmonary element clearly accentuated. There was a pulmonary ejection click and a short pulmonary systolic murmur There was no evidence of lung disease, mitral valve disease, or an intracardiac shunt due to congenital heart-disease. No abnormalities could be found in the remainder of the physical examination, which included pelvic examination. A radiograph of the chest showed an enlarged main pulmonary artery (fig 1) The cardiogram showed right ventricular hypertrophy, with a dominant R wave in lead V_4R, and T-wave inversion extending across to lead V_5 reminiscent of pulmonary vascular obstruction (fig 2a)

Other investigations included an erythrocyte-sedimentation rate, a full blood count, L.E.-cell preparations, serum-proteins, a male-toad test, and 5-hydroxy-indole-acetic-acid excretion. All results were within normal limits

Cardiac catheterisation (May 16, 1958) (see fig 3a) pulmonary artery pressure, 65/28 mm. Hg (mean 44 mm. Hg), mean pulmonary capillary venous pressure, 5 mm. Hg, cardiac output, 4 7 litres per min., pulmonary arteriolar resistance, 7 5 units (normal 0–2 units) Inhalation of 100% oxygen produced a drop of 20 mm. Hg in the systolic pulmonary artery pressure without alteration of the cardiac output, on

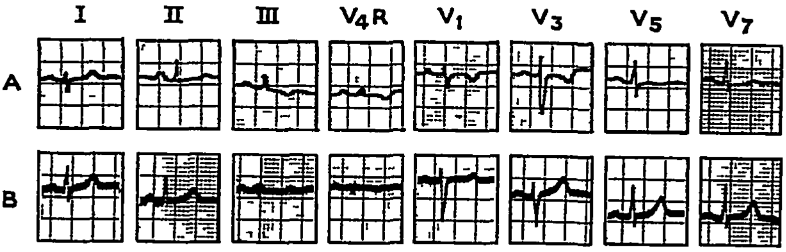

Fig 2—Cardiograms (A) before treatment with phenindione (March 20, 1958), (B) after five months' treatment (Aug 6, 1958)

After treatment the inverted T waves from V_1 to V_5 in A have become upright and the dominant R wave in lead V_4R has reverted to normal

withdrawal of 100% oxygen the pressure rose rapidly to the former level Injection of 5 mg of imidazoline ('Priscol') into the pulmonary artery had no effect on the pulmonary artery pressure, although the systemic pressure fell slightly The dye-dilution curves and the blood samples taken did not indicate the presence of any intracardiac shunt.

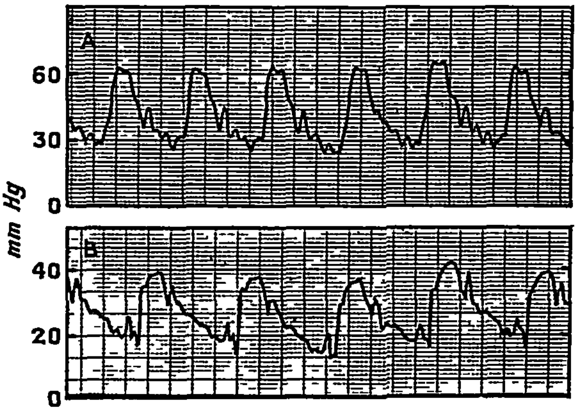

Fig 3—Pulmonary artery pressure A, May 16, 1958, B, Nov 6, 1959

Diagnosis

The data confirmed the presence of precapillary pulmonary hypertension due to disease of the arteriolar bed The absence of pulmonary venous hypertension, of an intracardiac shunt, and of lung disease suggested an obliterative process Since the patient was a young woman in whom the symptoms appeared shortly after childbirth, and since there was nothing to support a specific form of pulmonary arteritis, it was considered that the most likely cause was repeated pulmonary micro-embolism—probably from the pelvic veins There was no evidence of a puerperal cardiomyopathy The fall in pulmonary resistance on 100% oxygen encouraged the belief that the pulmonary vascular bed was not irreversibly damaged

Treatment and Course

The patient was stabilised on phenindione and asked to rest as much as possible at home She was also strongly advised against further pregnancies Prothrombin estimations were performed fortnightly, and the prothrombin-time was maintained at $2^{1}/_{2}$–3 times normal

Over the succeeding months she became symptom-free. The clinical signs of pulmonary hypertension gradually resolved Serial cardiograms showed regression of right ventricular hypertrophy until, five months after the patient's discharge from hospital, normal ventricular balance was restored (fig 2b) She was readmitted for further assessment in November, 1959, after eighteen months of continuous anticoagulant therapy She was now free of all symptoms On physical examination no abnormalities could be detected other than a very soft pulmonary ejection systolic murmur The second heart sound was normal Radiography still showed slight dilatation of the main pulmonary artery

A second cardiac catheterisation was performed on Nov 6, 1959 (fig 3), and the results are compared below with those obtained at the previous investigation

	May 16, 1958	*Nov 6, 1959*
Pulmonary-artery pressure (mm Hg)	65/28 (mean 44)	40/20 (mean 28)
Cardiac output (litres per min)	4·7	5·0
Pulmonary arteriolar resistance (units)	7·5	3·5

Clearly there had been a very significant drop in pulmonary artery pressure and pulmonary arteriolar resistance over the eighteen-month period. It was decided to withdraw gradually the anticoagulant drug and to keep the patient under very close supervision It was felt that, if no evidence of recurrence of pulmonary hypertension appeared over a period of six months a further pregnancy would probably not carry risk, though anticoagulant cover during and after the puerperium would be indicated Evidence of further thromboembolism did, however, appear, as is shown in fig 4

Cardiographs were repeated at monthly intervals The graph obtained five months after the suspension of therapy was clearly abnormal, the T waves in leads V_2 and V_3 being diphasic At six months there was T-wave inversion in leads V_2 and V_3, and restabilisation on phenindione was commenced

A month later T wave inversion had extended across to lead V_4, and on examination there was now a 4 cm "a" wave in the jugular venous pulse and a fourth heart sound was clearly audible at the left sternal edge Thereafter there was gradual improvement until, three months after the anticoagulant drug was recommenced, no abnormality could be found on physical examination and the electrocardiogram was once more normal The patient had remained completely symptom-free throughout It was decided to continue anticoagulant therapy indefinitely

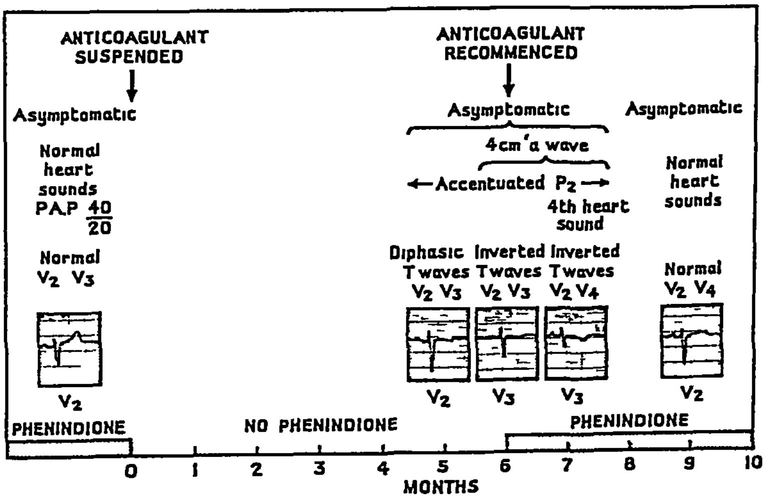

Fig 4—Clinical course after suspension of phenindione treatment.

P.A.P = pulmonary artery pressure

P_2 = pulmonary element of the second sound

Discussion

The abrupt onset of symptoms in a previously symptom-free woman and the regression of the pulmonary hypertension which accompanied treatment suggest that this was of recent onset. As regards ætiology, the differential diagnosis lay between "idiopathic" pulmonary hypertension and that produced by multiple silent pulmonary emboli. Other causes of recent onset of pulmonary hypertension were eliminated in this case clinically and by investigation.

Dexter (1957) has suggested that primary (or idiopathic) pulmonary hypertension should not be diagnosed during life as this implies therapeutic nihilism, and that all patients with pulmonary hypertension of undetermined cause should be treated as though they had recurrent emboli. He took the view that until necropsy has been performed recurrent pulmonary embolism could not be excluded—a view which we would support. There is, however, little doubt that our patient had thromboembolic pulmonary hypertension. The history is a classical one. Symptoms developed six months after a pregnancy. The long labour with a forceps delivery points to the pelvic veins as the source of the emboli, particularly as leg-vein thromboses were not noted. The favourable response to therapy makes unlikely, but does not completely rule out, the possibility of true "idiopathic pulmonary hypertension." A sustained reduction of pulmonary artery pressure has never been described with any form of treatment in a proven case of idiopathic pulmonary hypertension. The course is apparently always downhill and is modified only by the treatment of the inevitable right ventricular failure.

In our case it is most unlikely that recovery was spontaneous and unrelated to treatment, particularly as the physical signs of pulmonary hypertension and the electrocardiographic evidence of right ventricular strain returned after the suspension of anticoagulant therapy, and disappeared when this treatment was resumed. In the natural history of the disorder patients are commonly symptom-free until the pulmonary vessels are severely damaged. Symptoms occur relatively late, often at a level of pulmonary artery pressure much lower than is found, for example, in the Eisenmenger complex (Wood 1956), and once symptoms do develop the outlook is consistently bad (Owen et al. 1953). We infer that anticoagulant therapy in our patient cut short the extension of venous thrombosis in the pelvis, prevented further embolism, and promoted recanalisation of the already occluded pulmonary and pelvic vessels. Sevitt and Gallagher (1959), Honey and Truelove (1957), and many others have shown that phenindione effectively prevents venous thrombosis and pulmonary emboli, whilst Kubik and Payling Wright (1950) demonstrated that coumarin compounds speed the resorption of thrombi and the recanalisation, of vessels in rabbits.

There have been very few reported cases in which patients with established thromboembolic pulmonary hypertension recovered.

Two were recorded by Wood (1956). One patient was cured by long-continued anticoagulant treatment and strict bed rest after having been in right ventricular failure, the final cardiac catheterisation figures showing that the pulmonary resistance had been restored to normal. In the second case the pulmonary artery pressure fell significantly, although not to normal. Dexter (1957) cited a case in which anticoagulants were given for two months. The patient had an impressive clinical improvement and remained active for seven years, though subsequent catheterisation did not show any fall in the pulmonary artery pressure.

Burchell et al (1950) showed that inhalation of 100% oxygen will cause dilatation of the pulmonary arterioles. In our patient the pulmonary artery pressure fell whilst 100% oxygen was inhaled and returned promptly to the previous level when it was withdrawn, the fall in pressure being unaccompanied by a fall in output. The vessels therefore were still capable of dilatation. It has been established that in certain types of "idiopathic pulmonary hypertension" there is active vasoconstriction which can be temporarily reversed. Dresdale et al (1951) produced significant falls in pulmonary artery pressure by direct injections of imidazoline into the pulmonary artery, the cardiac output either rising or remaining steady, and Wood (1956) did likewise using acetylcholine. Although Daley (1957) was unable to demonstrate generalised pulmonary vasoconstriction after localised pulmonary embolism Price et al. (1955), from a series of well-devised experiments in dogs, claimed that intense constriction of the lung vessels results from acute miliary pulmonary embolism and that this is neurogenic in origin, mediated by the sympathetic.

It has not been possible to lower the pulmonary artery pressure of patients with congenital pulmonary hypertension and reversed shunt after the age of 5 years with any of the agents cited above (Wood 1958), the inference being that in these cases the pulmonary vessels have become so damaged that dilatation is no longer possible. Hence the fall in pressure in our patient indicated the presence of some potentially reversible vasoconstriction and was a good prognostic feature, which was subsequently confirmed by the response to treatment.

The recurrence of symptomless thromboembolic pulmonary hypertension some time after the cessation of a long course of effective anticoagulant treatment which had been accompanied by a very satisfactory hæmodynamic response has not previously been recorded. Such continuing small-vein thromboses with repeated minute pulmonary embolism may well be the underlying cause in a significant proportion of cases of pulmonary hypertension otherwise termed "idiopathic" or "primary".

Summary

In a case of established thromboembolic pulmonary hypertension a very satisfactory symptomatic and hæmodynamic response was produced by long-term anticoagulant therapy.

Five months after the cessation of therapy the signs of pulmonary hypertension reappeared, though the patient remained symptom-free, these signs disappeared when anticoagulant therapy was reinstituted.

Before treatment was begun, the pressure fell when the patient breathed 100% oxygen.

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STABLE IODINE METABOLISM IN NON-TOXIC GOITRE

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NON-TOXIC goitre occurs both endemically and sporadically The balance of evidence favours the view that the endemic form results from iodine deficiency, and the investigations of Stanbury et al (1952), using modern techniques, have confirmed this opinion The cause of sporadic non-toxic goitre is still, however, the subject of controversy (*Lancet* 1958, *Scottish Medical Journal* 1959) It has always been difficult to explain why some members of a community should develop goitre when all are taking apparently similar diets Various ætiological factors have been suggested, operating either alone or in combination, including contaminated water-supplies, virus and other infections, and goitrogens or excess calcium in the diet Recently it has become clear that some cases of non-toxic goitre are really examples of euthyroid Hashimoto's disease

Stanbury et al (1950, 1957) have shown that goitrous cretins may have deficiencies in the enzyme systems of the thyroid gland which are necessary for the normal synthesis of thyroxine These observations have been extended to cases of sporadic goitre, and, at least in some cases, similar factors are operative (Stanbury et al 1956, McGirr et al 1959) McGirr (1960) has therefore put forward the view that dyshormonogenesis may be a major factor in this condition, and that iodine deficiency, if it is implicated at all in the United Kingdom is more likely to play a subsidiary than a principal role

In endemic goitre, evidence of iodine deficiency is afforded by a raised uptake of radioactive iodine (^{131}I) associated with a normal level of plasma protein-bound radioactive iodine (P B ^{131}I), a normal level of chemical protein-bound iodine (P B I), and a low daily urinary iodine excretion (Stanbury et al 1952) These studies do not, however, give a complete picture of iodine metabolism, and this can be obtained only if, in addition, the plasma inorganic iodine (P I I) is estimated One can then calculate the absolute iodine uptake (A I U) by the thyroid gland, and see whether a high uptake of radioactive iodine is the result of iodine deficiency with a rapid turnover of the available iodine, or an incapacity of the gland to synthesise fully a normal amount of circulating iodine If low P I I levels are found, iodine deficiency is clearly present

By combining all these investigations we have obtained a very full picture of total iodine metabolism in twenty-one patients with sporadic goitre not due to any known cause, in an area free from endemic goitre and (what is even more important) one in which iodised salt is rarely used A control group of subjects without goitre and without evidence of thyroid disease was investigated by the same techniques

Methods

The diagnosis of simple non-toxic goitre was made after full clinical and laboratory investigation to exclude, as far as possible, known causes of goitre such as thyrotoxicosis, neoplasm, thyroiditis, and dyshormonogenesis

All twenty-one patients were women, and their ages ranged from 16 to 59 years (mean 35) Eight (38%) gave a family history of goitre All except three had been born in or near Glasgow, one was born in England, one in Czechoslovakia, and one in Ireland, but all had been living in the Glasgow area for several years The precipitin test for thyroid autoantibodies was negative in all cases

Thirteen patients without evidence of endocrine disease were chosen as controls All had normal thyroid function, as judged by clinical observation, radioactive-iodine studies, and plasma P B I levels All took their normal diet, but fasted on the day of the radioiodine and stable-iodine tests

Radioactive iodine was used as the shortlived isotope ^{132}I in seventeen of the goitrous cases and eleven of the normal subjects, and as ^{131}I in the remainder The radioactive iodine (supplied by the Radiochemical Centre, Amersham) was proved to be free from carrier iodine ^{127}I Inaccuracy in the thyroid-uptake measurement due to back-scatter radiation was eliminated by checking the results with a "phantom" thyroid The thyroid-gland uptake measurements using ^{132}I and ^{131}I were comparable

The rate of clearance of radioactive iodine from the thyroid gland was measured according to the method of Myant et al (1949), between 1 and 2$^1/_2$ hours after the oral administration of 25 µC of ^{131}I or 50 µC of ^{132}I Simultaneous estimation of the radioiodine and stable-iodine content of the urine excreted over the same period provided data for the estimation of the P I I and the A I U by the thyroid gland, using the method of Stanley (1949) The P I I (in µg per 100 ml) was calculated from the formula

$$\text{P I I} = \frac{\text{I-urine} \times {}^{131}\text{I (or } {}^{132}\text{I)-plasma}}{{}^{131}\text{I (or } {}^{132}\text{I)-urine}}$$

where I-urine represents the stable iodine of the urine in µg per 100 ml, ^{131}I-plasma the radioiodine content of the plasma in % of dose per ml plasma, and ^{131}I-urine the radioiodine content of the urine in % of dose per ml urine

The accuracy of the indirect estimation of P I I was confirmed by direct chemical determination (Richmond et al 1960) in six cases in which it was large enough The difference between the direct and indirect estimate did not exceed 15%

The A.I U in µg per hour was calculated from the formula

$$\text{A I U} = \text{P I I (µg per ml)} \times \text{thyroid clearance of radioiodine (ml per hr)}$$

The renal clearance was calculated in the same way as the thyroid clearance, using the urinary excretion instead of the thyroid uptake of radioactive iodine

The intrathyroid exchangeable iodine (I E I) was estimated by the method of Nodine et al (1957) using an injection of 10 units of thyroid-stimulating hormone given on the 10th day after administration of 75 µC of ^{131}I Serum P.B I results were obtained with a modified chloric-acid-digestion method (Richmond et al 1960) Urinary iodine was estimated on 0 5–1 0 ml aliquots by the same chemical reaction, but without prior treatment The mean recovery of iodine added to urine was 99 3% (S D ± 3 7%) The absence of significant amounts of organic iodine in the urine was confirmed by the use of an anion-exchange column (Richmond et al 1960)

The iodine content of the diet was assessed from histories taken by one experienced dietitian, using tables issued by the Chilean Iodine Educational Bureau (1952)

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Results

Thyroid uptake and clearance of radioactive iodine—The radioactive iodine uptake in the group of patients with goitre (mean 39 9%) was significantly higher than the control group (mean 25 6%) The mean thyroid clearance in the former group (61 6 ml per min) was also significantly higher than in the control group (23 0 ml. per min) In eight of the twenty-one goitrous cases the uptake of radioactive iodine was above 40%, and in twelve cases the thyroid clearance of radioactive iodine was above the normal limit (40 ml per min)

Plasma inorganic iodine—Of the twenty-one cases with goitre, sixteen had P I I levels of 0 02–0 09 µg per 100 ml. whereas the lowest value in the control group was 0 10 µg per 100 ml. The remaining five cases had values in the low normal range The difference in the mean values of the goitre group (0 07 µg per 100 ml), and of the control group (0 30 µg per 100 ml) is significant

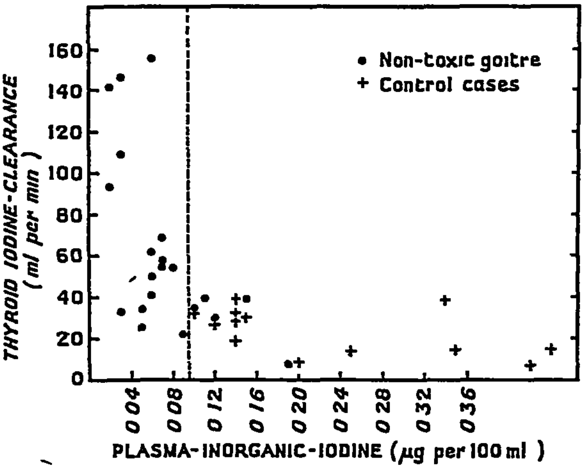
The best estimate of significance is given by a t test after logarithmic conversion of the values, since these fit a lognormal distribution (t=5 53, P <0 001) ‡

Absolute iodine uptake—The A.I U (2 2 µg per hr) of the goitre group was slightly lower than that of the control group (2 9 µg per hr), but the difference is not significant The control values agree with the data recorded by Burrows and Ross (1953), Fauvert et al (1958), and Reilly et al. (1958) using the same methods, and with the data of Ingbar and Freinkel (1955) and Nodine et al. (1957) using different ones

Chemical and radioactive protein-bound iodine—The mean P B I was the same in both groups The P B ^{131}I was normal in all the goitrous cases (<0 30% dose per litre) except one, which had a P.B ^{131}I of 0 47% per litre but a normal P.B I, a normal gland suppression after 0 2 mg l-thyroxine daily, and a negative precipitin test.

Renal clearance of radioactive iodine and urinary iodine excretion—The 24-hour urinary iodine excretion was low in the goitre group (mean 59 µg per day) as compared with the control group (mean 91 µg per day) The renal clearance of radioactive iodine was slightly, but not significantly, higher in the goitrous group

Intrathyroid exchangeable iodine—In three patients with simple goitre the intrathyroid exchangeable iodine was 6 2, 10 0, and 14 6 mg respectively, while in two normal subjects the values were 11 0 and 13 4 mg This suggests that these goitres contain a normal amount of iodine in an increased tissue mass



Relation between thyroid iodine-clearance and plasma-inorganic-iodine.

The dotted line indicates the lower limit of the plasma-inorganic-iodine in the control group

Correlation between P I I and thyroid clearance of radioiodine—The relation between P I I and clearance was examined (see figure) Cases with a low P I I had in general a high clearance (r=—0 43, t=2 70, P <0 02, without logarithmic conversion, r=—0 40, t=2 47, P <0 02)

Discussion

Our results show clearly that in comparison with a normal control group a large proportion of people with non-toxic goitre have low P I I levels Reilly et al (1958) have also estimated P I I levels in an extensive series which included seven cases of non-toxic "nodular goitre" But unfortunately even 2 years ago the importance of excluding cases of Hashimoto's disease, and of recognising dyshormonogenesis, was not appreciated Moreover the widespread use of iodised salt in North America makes the interpretation of their results difficult. This may be the reason why the P I I levels in our control group were lower than those recorded in the normal cases in the series of Reilly et al But we have confirmed the observations of these workers that the P I I is normal in thyrotoxicosis, we have also found normal P I I values in cases of Hashimoto's disease and dyshormonogenesis (Koutras et al 1960) In our experience, therefore, a low P I I is characteristic of the group with non-toxic goitre and is found in no other thyroid disorder, even when the turnover rate of inorganic iodine is high.

The low P I I levels in our cases of non-toxic goitre could be due to three causes—a low intake of iodine in the diet, a diminished absorption of iodine, or an abnormal

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‡ The validity of this conclusion is independent of distribution Without logarithmic conversion, t = 2 84, P<0 01 By applying the χ-square test to the incidence of low P I I in the two groups, χ^2 = 15 68, P<0 001

RESULTS AND STATISTICAL ANALYSIS

Investigations	Control cases (13)			Goitrous cases (21)			Difference between means		
	Mean	S.E.	Range	Mean	S.E.	Range	Goitre-control	t	P
Thyroid radioiodine uptake at 2½ hours (% of dose)	25 6	2 4	16 2–43 0	39 9	2 6	23 9–74 1	+14 3	4 06	<0 001
Thyroid radioiodine clearance (ml. plasma per min.)	23·0	2 8	6·6–38 0	61 6	9 1	7 3–155 4	+38 6	4·05	<0·001
P.I.I. (µg. per 100 ml.)	0·30	0·08	0 10–1 09	0·07	0·01	0·02–0 19	− 0·23	5 53	<0 001
A.I.U by the thyroid (µg per hour)	2 9	0 5	1·0–8 2	2 2	0·3	0 7–5 7	− 0·7	1 24	0 25
P.B.I. (µg. per 100 ml.)	5 1	0·3	3 1–6·6	5 2	0·3	2 7–8 3	+ 0·1	0·25	0 8
Renal radioiodine clearance (ml plasma per min.)	33 3	2 6	20·4–53 8	37 8	2 6	16 0–63 7	+ 4·5	1 23	0·25
Urinary iodine excretion (µg. per day)	91 0	11 0	44–153	59 0	8 0	30–92	−32·0	2 34	<0·05
Intrathyroid exchangeable iodine (mg.)	12 2		11 0–13 4	10·3		6 2–14 6			
Mean dietary iodine intake (µg per day)	116·0	16·0	48–198	75 0	16 0	16–142	−41·0	1 81	<0 1

The daily urinary iodine excretion and the mean dietary intake of iodine were estimated in eight cases of each group, and the intrathyroid exchangeable iodine in three goitrous and two normal cases

The t test for the difference between the mean P.I.I values was calculated after logarithmic conversion.

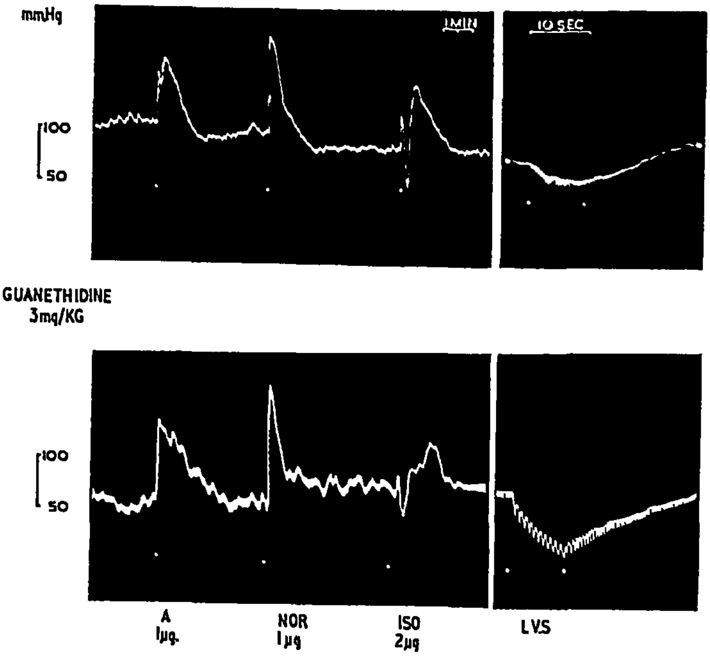

Fig 1.—(Cat, 2·8 kg.) Blood-pressure responses to adrenaline (A) noradrenaline (NOR), isoprenaline (ISO), and to vagal stimulation (LVS) before (upper tracing) and 3 hours after (lower tracing) the intravenous administration of guanethidine 3 mg. per kg.

L.V.S. = left vagus stimulation at 10 shocks per sec. for 10 sec.

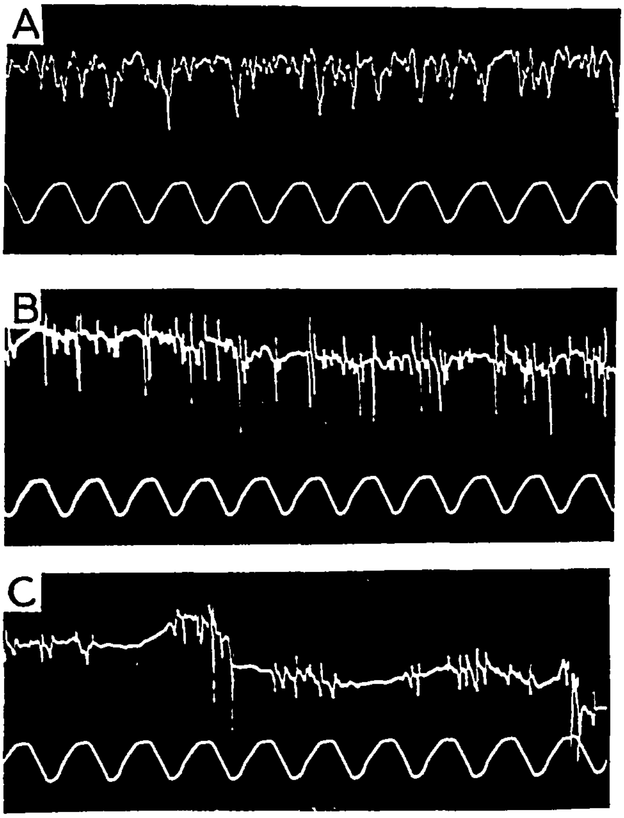

Fig. 3.—Electromyograms of motor-unit action-potentials.

A. Pattern of normal motor-unit action-potentials from tibialis anterior of a cat.

B. Same muscle after treatment of the cat with bretylium tosylate 5 mg. per kg. per day for five days.

C. Similar recording from another cat treated with guanethidine 0·5 mg. per kg. per day for six days.

Calibration wave 200 µ volts at 50 cycles per second.

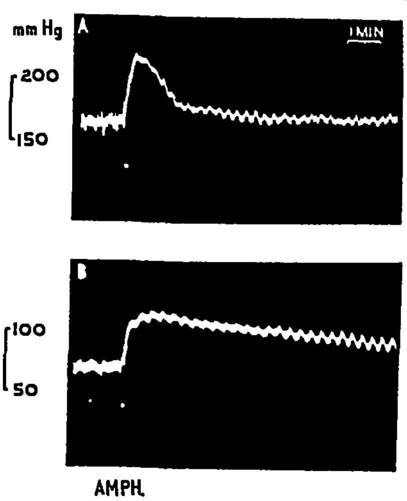

Fig. 2.—Blood-pressure responses to 0·3 mg. per kg. amphetamine sulphate.

A. Cat, 2·4 kg. Bretylium pretreated, 20 mg. per kg. for 2 days.

B. Cat, 2·8 kg. Guanethidine pretreated, 8 mg. per kg. for 2 days.

At this stage, stimulation of the cervical sympathetic nerve to the nictitating membrane produced no effect.

guanethidine special care should be taken of patients with impaired heart activity or of patients who are likely to go through a period of excessive heart stimulation, for instance during anæsthesia and surgical procedures.

From the start, we were impressed by the striking similarity between some of the responses obtained from animals under the influence of bretylium or guanethidine and those obtained in untreated animals whose body-temperature had been lowered. When the body-temperature is reduced gradually from 38° to 30°C, the effect of adrenaline, noradrenaline, and isoprenaline on the blood-pressure is increased and prolonged. In general, the duration of action is more affected than the magnitude of the response. At the same time the effect of vagal stimulation on the heart is potentiated and the duration of a block produced by depolarising drugs greatly prolonged (Cannard and Zaimis 1959). Furthermore, a phasic variation in the blood-pressure pattern initiated by isoprenaline, by adrenaline, and to a lesser extent by noradrenaline, also occurs in animals at lowered body-temperatures. In addition, both lowering of body-temperatures and the administration of bretylium or guanethidine affect the response to adrenaline more than that to noradrenaline.

In a recent article on the action of drugs known to affect adrenergic mechanisms (Zaimis 1960) the resemblance between the changes produced by cooling alone and those produced by such drugs was discussed and a possible common metabolic basis for their mechanism of action was suggested.

We thank Burroughs Wellcome & Co. for the supply of bretylium and Ciba Laboratories Ltd. for guanethidine. The work was performed during the tenure by one of us (J. V.-D.) of a Smith, Kline & French fellowship.

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MUSCLE WEAKNESS CAUSED BY BRETYLIUM TOSYLATE

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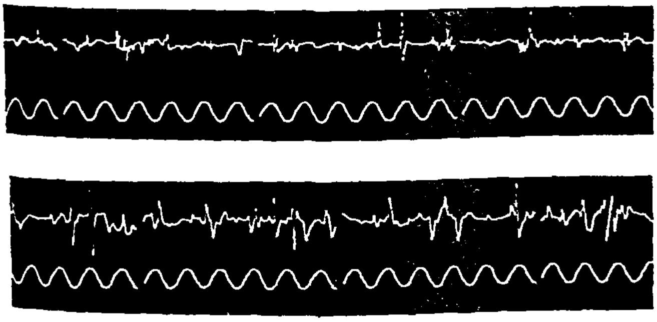
MUSCLE fatigue occasionally troubles patients treated with bretylium tosylate In some cases a precipitate fall in blood-pressure on moderate effort (Lowe and Rosenheim 1960) may explain this symptom, but in others this explanation is inadequate Evanson and Sears (1960) report a case in which the electromyogram showed an abnormal pattern, and Evanson in a personal communication has stated that a myopathic pattern was in fact found We now present the detailed investigation of a similar case

Case-report

A man of 64 had been treated for severe hypertension since 1956 with mecamylamine. Because of side-effects (dryness of the mouth and severe constipation) the treatment was changed in October, 1959, to bretylium tosylate 1 8 g daily in divided doses with an added oral diuretic (dehydrofluomethiazide) Within a few days he complained of severe muscular weakness especially in the shoulder girdle, so that he found it difficult to comb his hair and shave Towards the end of the day he had difficulty in opening his eyes and swallowing He also complained of increased breathlessness on exertion walking quickly up three flights of stairs produced breathlessness but no significant fall in blood-pressure

There were no signs of congestive cardiac failure, an X-ray of the chest showed neither further enlargement of the heart nor pulmonary congestion, and the arm-to-tongue circulation time was 14 seconds Pulmonary-function studies showed moderate diminution in vital capacity and forced expiratory volume, this being accounted for by old tuberculous disease which had caused obliteration of the left pleural space and pulmonary fibrosis The blood-urea remained constantly raised to between 70 and 80 mg per 100 ml but there was no hypokalæmia.



Electromyograms

Upper tracing from vastus medialis of patient during bretylium therapy

Lower tracing from vastus medialis of patient six weeks after bretylium therapy had been stopped.

Calibration wave—300 µ V at 50 cycles per second.

Because of the widespread muscular weakness, the function of the lower motor neurones and muscle-fibres was investigated in detail. An electromyogram (E.M G) from the right deltoid and right vastus medialis showed a myopathic pattern with disintegration and shortening of the motor-unit action-potentials (see figure) Peripheral and terminal nerve-fibre involvement, as may be seen in neuromyositis, seemed unlikely as intensity-duration curves were normal and there were no spontaneous fibrillation-potentials on the E M G

In view of the myasthenic features of some of his symptoms the diagnosis test for myasthenia gravis described by Churchill-Davidson and Richardson (1953) was performed After 2 5 mg of decamethonium iodide had been given intravenously over 6 minutes the patient was almost incapable of voluntary movement and the action-potentials obtained from the hypothenar muscles on supramaximal stimulation of the ulnar nerve at 10 shocks per second were greatly reduced. This is the expected finding in a normal person.

Treatment was then changed from bretylium tosylate to guanethidine 75 mg per day, and within one week there was considerable subjective improvement in muscle power, and in ability to perform tasks which were previously impossible, such as using the garden shears He was also less breathless, although further pulmonary-function studies failed to show any significant change The E M G a fortnight after the change of treatment was still abnormal though the degree of abnormality seemed less By the end of six weeks, however, without further change of treatment, the pattern had returned to normal (see figure)

Discussion

From these results it seems clear that bretylium may produce derangement of muscle-cell function by direct action and not through circulatory changes The E M G from the experimental animals (Vernikos and Zaimis 1960) and from our patient were taken by the same observer and show the following similarities in both the duration of muscle action-potentials is shortened to *1–2 msec, compared with the normal range of 5–7 msec* in the human quadriceps, and 3–5 msec in the cat tibialis anterior, amplitude is not significantly changed In both the cat and the human these changes occurred in patches throughout the bulk of the muscle in much the same way as in other myopathies, typical examples of the characteristic changes in the E M G have been chosen for illustration These changes indicate that a number of muscle-fibres in each anatomical motor unit are not functioning They are non-specific They may be caused by a variety of mechanisms—degeneration of muscle-fibre in muscular dystrophies and in polymyositis, or biochemical disturbances such as potassium deficiency in familial periodic paralysis The mechanism of the present disorder is not yet understood, but Zaimis (1960) has suggested that adrenergic systems may be concerned in the recovery of muscle after contraction and that these are probably affected by bretylium

Summary

A case of muscle weakness produced by bretylium tosylate is presented.

The weakness is shown on electromyographic evidence to be due to the lack of function of a proportion of muscle-fibres within each motor unit.

A comparison is made with similar changes produced under experimental conditions

We should like to thank Dr B J O Winfield for the pulmonary-efficiency studies and Dr A. T Richardson for permission to report the E M G findings

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AN OUTBREAK OF ACUTE LARYNGOTRACHEOBRONCHITIS ASSOCIATED WITH PARAINFLUENZA-2 VIRUS

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PARAINFLUENZA-2 virus was first described by Chanock (1956), who named it the croup-associated or C A virus He isolated two strains from twelve children under the age of 3 years, with croup The two children from whom the strains were isolated responded well serologically to the agents Besides these were a further four children who showed serological evidence of having been infected

Beale et al (1958), working in Toronto, reported the isolation in 1955 of ten strains of an agent associated with acute laryngotracheobronchitis in fifteen infants and children under 3 years These strains proved to be serologically identical with the C A virus isolated by Chanock The name parainfluenza-2 has been proposed for this virus (Andrewes et al 1959)

In a small serological survey of children and young men in Washington, Chanock found that 25% of infants and 90% of young adults had hæmagglutination-inhibiting antibody to C A virus, which suggested frequent infection with this virus early in life and during childhood

It is remarkable, in view of this finding, that reports of its isolation have been so few Cramblett (1958), isolated one strain from a 4-month-old infant with croup, and, in a review of respiratory infection, Ward (1959) referred to the isolation of five strains in Washington, D C In Europe the isolation of parainfluenza-2 has not been reported, although in an antibody survey in Sheffield (Clarke and Gaynor 1959) 33% of children under the age of 8 were found to have hæmagglutination-inhibiting antibodies

In this report we describe an outbreak of acute laryngotracheobronchitis in North East Kent, apparently caused by the parainfluenza-2 virus

The Outbreak

A number of cases of acute laryngotracheobronchitis were seen in children in the Chatham and Rochester area of Kent at the end of October, 1958 Thirteen of these children were admitted to hospital, two in October, three in November, four in December, and four in January

Their ages ranged from 4 months to 4 years Four children were under 1 year, and five were 1 year, one was 2 years, and three were 4 years old There were eleven boys and two girls All but one boy recovered One child became ill after contact with cases of acute laryngotracheobronchitis in hospital

Acute laryngotracheobronchitis usually followed abruptly after an upper respiratory infection causing a croupy cough, hoarse voice, and inspiratory stridor which led to a variable amount of respiratory distress, often severe enough to cause supraclavicular and subcostal recession, and to produce cyanosis The respiratory-rate was always increased, but the temperature was not necessarily raised The throat was injected but no membrane was detected Signs in the lung varied, but in severe cases the air entry was poor and scattered ral and rhonchi were present Most of the children we nursed in a steam tent and given chloramphenicol.

The following are the case-histories of three patients i whom evidence of infection was established either b virus isolation or by serological tests, and of a fatal cas

THE FIRST CASE

This boy, aged 7 months, was admitted to hospital on Jan 1959, having had a head cold for 3 days, followed 2 days lat by stridor and a barking cough, with restlessness, fever, an slight diarrhœa

On admission he was ill but well nourished, weighing 20 l The rectal temperature was 102°F, and the respiratory-rate wa 50 per min., with a noisy inspiratory stridor Nasal discharg was profuse, subcostal recession was present, and coarse crepitations were heard in both lung fields

Investigations —Heaf tuberculin skin test, negative, hæmoglobin, 72%

Treatment and progress —The infant was put in a steam tent and given chloramphenicol 250 mg 6-hourly for 5 days His pyrexia slowly subsided, and the stridor and signs in the chest rapidly disappeared, but he remained hoarse for a week On the 7th day his temperature rose to 101 6°F although his chest was clear on examination After a 3-day course of streptomycin 125 mg and penicillin 125,000 units twice daily intramuscularly, the child made an uninterrupted recovery

THE SECOND CASE

This boy (the 4-year-old brother of the first case) was admitted to hospital on Jan 5, 1959, having had a cough for 4 days which a few hours previously had become associated with stridor

On admission he was well nourished, with a temperature of 98 6°F His respiratory rate was 30 per min He had inspiratory stridor, a harsh barking cough, and supraclavicular recession No adventitious sounds were present in the lung fields The tonsils and larynx were injected.

Investigations —White-cell count 8000 per c mm (polymorphs 66%, lymphocytes 33%, monocytes 1%), erythrocyte-sedimentation rate (Westergren) 11 mm in the 1st hour, hæmoglobin 87%, chest X-ray showed extensive right hilar shadows, Heaf tuberculin skin test, negative

Treatment and progress —Chloramphenicol 250 mg was given 6-hourly for 24 hours, followed by 125 mg 6-hourly for 5 days He was nursed in a steam tent, with tinct benz co, and given chloral as a sedative He made a satisfactory recovery although he remained hoarse for 4 days

THE THIRD CASE

This girl, aged 4 years, was admitted to hospital on Dec 19, 1958, having had a cold for a day, followed by a severe croupy cough and increasing breathlessness

On admission she was ill but well nourished, with a temperature of 100°F The respiratory rate was 40 per min, with inspiratory stridor and supraclavicular and subcostal recession. The air entry was poor, with inspiratory rhonchi The throat was injected but no membrane was present The heart sounds were faint and rapid. Coughing produced thick tenacious sputum

Investigations —Heaf tuberculin skin test, negative, throat swabs revealed no bacterial pathogens

Treatment and progress —The child was nursed in a steam tent with tinct. benz co, and given chloramphenicol 400 mg intramuscularly, followed by 375 mg 6-hourly for 24 hours, and then 200 mg 6-hourly for 3 days Despite this treatment, and sedation with chloral, she became increasingly ill, with cyanosis and breathlessness 12 hours after admission she was placed in an oxygen tent with an aerosol mist ('Alevair') Because of tachycardia and feeble heart sounds digoxin was given The child slowly improved, and after being nursed in a steam tent for 3 more days she made an uninterrupted recovery

THE FATAL CASE

This boy, aged 11 months, was admitted to hospital on Nov 22, 1958 He had had a cough with increasing difficulty in breathing for 4 days, and this had become worse depite treatment with penicillin

On admission he was pale, cyanosed, and desperately ill, with a temperature of 99 6°F His respiratory rate was 40 per min, with intercostal and supraclavicular recession and a tracheal tug The air entry was very poor over both lung fields, and inspiratory laryngeal stridor caused extreme respiratory distress

Treatment—Tracheotomy was done within 30 minutes of admission, with some improvement Although he was nursed in oxygen with alevair, and was given chloramphenicol 250 mg 6-hourly intramuscularly, he became increasingly restless and suddenly collapsed and died 6 hours later No material was examined post mortem

LABORATORY EXAMINATIONS

Virus Investigations

HeLa cells, monkey-kidney cells, and human amnion-cell cultures were prepared and maintained by methods previously described (Holland et al 1960) 0 1 ml amounts of the throat-swab materials were inoculated into duplicate tubes of each tissue-culture system, which were then incubated at 37°C until evidence of a cytopathic effect appeared Monkey-kidney tubes were tested at 5-day intervals for hæmadsorption by adding 0 2 ml of 0 4% suspension of guineapig erythrocytes Strains isolated were identified by serum-neutralisation tests in monkey-kidney cultures, by means of serum from rabbits hyperimmunised with parainfluenza viruses

Complement-fixation Tests

These were done in 'Perspex' hæmagglutination trays, with 0 1 ml unit volumes and overnight fixation at 4°C The antigen was culture fluid from monkey-kidney cells infected with parainfluenza-2 virus, standardised by chess-board titration against human convalescent serum, and used at an optimal dilution

Throat swabs from five children were examined by the methods described. Two of the swabs yielded a virus which was detected by the hæmadsorption technique in monkey-kidney tissue cultures after 5 days' incubation at 37°C The characteristic effect on the cells of both monkey-kidney and human-amnion cultures was only seen after incubation for a further 4–8 days This cytopathic effect comprised the formation of syncytial masses and the development of large holes in the cell sheet Both hæmadsorption viruses were neutralised by parainfluenza-2 rabbit antiserum to the same titre as the prototype parainfluenza-2 strain received from Dr R M Chanock A fourfold rise in complement-fixing antibodies to the virus isolated was detected in two pairs of sera available

The results of isolation and serological examination of the available specimens are shown in the table

One strain of parainfluenza-2 virus was isolated from a throat swab taken on the 5th day of illness of the first child Serum was not available for tests Virus was not isolated from the throat swab from his brother (the second case) taken on the same day of illness, but his serum showed a rise in complement-fixing antibodies from < 1/4 to 1/64 A throat swab from the third child taken on the 2nd day of illness yielded the second strain of virus, and her serum showed a rise in complement-fixing antibodies from < 1/4 to 1/128

Besides the isolation of strains of parainfluenza-2 virus reported here a further strain was isolated from a child with a respiratory infection in Cardiff In the north of England Gardner et al (1960), in a survey of respiratory illness in children, reported the isolation of five strains Further studies are required to determine how often this virus is associated with acute laryngotracheobronchitis in this country

VIROLOGICAL FINDINGS IN THREE PATIENTS WITH *ACUTE LARYNGOTRACHEOBRONCHITIS*

Cases	Age (yr)	Parainfluenza-2 virus isolation	Serological response to parainfluenza-2 virus	
			Day of disease	Complement-fixing antibody titre *
1	$^{7}/_{12}$	+		No serum available
2	4	−	4	<4
			12	64
3	4	+	2	<4
			11	128

* Titre expressed as reciprocal of initial serum dilution.

Summary

Thirteen children aged 4 months to 4 years were admitted to hospital with acute laryngotracheobronchitis Parainfluenza-2 virus was isolated from two of six throat swabs examined Serological evidence of infection with this virus was obtained in two patients from whom paired serum specimens were available

We should like to thank Dr J H. C Walker of the Public Health Laboratory, Maidstone, for his cooperation.

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PROTECTION OF MICE AGAINST ASIAN INFLUENZA-VIRUS INFECTION BY A NORMAL HORSE-SERUM INHIBITOR

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The efficacy of influenzal immune serum, administered by parenteral injection, in protecting mice against experimental influenza was clearly established by Laidlaw et al (1935) Subsequently Smorodintseff (1939) and Stokes and Shaw (1939) showed that effective protection was also afforded by immune serum given intranasally Some success in the prophylactic and therapeutic use of immune sera in man has been reported by Smorodintseff (1939), Smorodinzew et al (1940) and Zhdanov (1959), but the pronounced antigenic lability of influenza viruses, together with the difficulty of preparing large quantities of potent antisera, limit the potentialities of the method and have prevented its adoption on a large scale Nevertheless the principle of preventing initiation of infection by the intranasal instillation of a substance capable of combining with extracellular virus remains attractive

A substance present in normal horse serum, which inhibits hæmagglutination and neutralises infectivity of many Asian influenza strains has been described recently (Shimojo et al 1958, Cohen and Belyavin 1959) It is distinct in its biological properties from inhibitors of the α and β types (Francis 1947, Chu 1951, Smith et al 1951) and the term γ-inhibitor is proposed for this substance It differs from other normal serum components which neutralise infectivity of influenza viruses (Ginsberg and Horsfall 1949, Smith and Westwood 1949, Chu 1951, Briody et al 1955) in its high potency This suggested the investigation of normal horse serum as a prophylactic and therapeutic agent in experimental influenza infection Studies were hampered at first because adaptation of Asian strains to the most convenient laboratory test animal—the mouse—resulted on some occasions in acquisition of resistance to the inhibitor (Cohen and Biddle 1960) But mouse adaptation with retention of inhibitor sensitivity was achieved, thus providing a virus strain suitable for the purpose in view

Materials and Methods

Viruses

Inhibitor-sensitive variant—A variant derived from the A/Singapore 1/57 strain after an unknown number of allantoic passages in embryonated hens' eggs and 53 passages in mice This virus was used in all the mouse protection tests

Inhibitor-resistant variant—Another variant derived from the A/Singapore 1/57 strain after an unknown number of allantoic passages and 30 passages in mice

Seed viruses in the form of 10% mouse-lung suspensions in broth-saline were stored at −70° C in capillary tubes

For hæmagglutination and hæmagglutination-inhibition tests, infected allantoic fluids were prepared by inoculation of 10–12-day old embryonated hens' eggs with 0 2 ml inocula of seed virus diluted 10^{-3} in nutrient broth containing penicillin 2500 units per ml, and streptomycin 3000 µg per ml After incubation at 35°C for 48 hours, the eggs were chilled overnight and the allantoic fluids were harvested, pooled, and stored at 4°C until required

Sera

Horse—A single batch of pasteurised horse serum (' Wellcome ' brand no 2) stored at −20°C was used throughout the investigation

Bovine—Normal bovine serum, stored at −20°C was used uninactivated

Rabbit—Normal and immune sera were obtained from a single rabbit The immune serum was prepared by intravenous injection of the A/Singapore variant virus described by Cohen and Belyavin (1959) Two injections of approximately 100 and 1000 hæmagglutinating doses were given at an interval of 3 weeks Immune serum was collected 14 days after the second injection

Normal and immune rabbit sera were freed from non-specific inhibitors by treatment with crude receptor-destroying enzyme (R D E) One volume of serum was mixed with two volumes of R D E diluted 1 2 in calcium-acetate-buffered saline, held at 37°C for 5 hours, and then at 56°C for 30 minutes to inactivate the R D E After treatment with R D E the sera were absorbed with chorioallantoic membrane (C A M) to remove antibody to the host-tissue component (Smith et al 1955) Membranes were harvested from 11- or 12-day-old embryonated hens' eggs, washed thoroughly in three changes of physiological saline, and minced with scissors After suspension in a suitable volume of saline the minced C A M, was sedimented by centrifugation at 3000 g for 20–30 minutes resuspended in a suitable dilution of the serum to be absorbed, and held at 4°C overnight. Next day the minced C A M was resedimented by centrifugation, the supernatant fluid constituted the absorbed serum

Periodate Treatment

1 ml of serum diluted 1 5 was mixed with 1 5 ml of M potassium periodate in saline and held overnight at 4 Next day 1 5 ml of a 10% glucose solution in saline was ad to neutralise any excess periodate

Hæmagglutination and Hæmagglutination-inhibition Titrations

Titrations were performed by the photoelectric densitome method of Hirst and Pickels (1942), modified by Smith, a Westwood (1949) and Belyavin et al (1951) Titres we obtained from densitometer readings by the use of Lin nomogram for 50% end point interpolations (Lim 1954)

Mouse Inoculations

All intranasal inoculations of virus and horse serum we carried out under ether anæsthesia Intravenous inoculatio were performed without the aid of anæsthesia

Virus Titrations in Mice

Serial 10-fold dilutions of seed virus in 50% broth-sal were inoculated into groups of six 12–18 g Swiss albino mic the inoculum volume was 0 05 ml After an observatio period of 10 days the 50% lethal dose was calculated by t method of Thompson's moving averages (Thompson 194 No significant loss of infectivity on storage was noted duri the investigation

Total Lung-lesion Score

At the end of the 10-day observation period mice remaini alive were killed and their lungs examined for typical influen lesions These were scored as follows 5 for complete co solidation and death, 4 for complete consolidation, 3, 2, and for $^3/_4$, $^1/_2$, and $^1/_4$ consolidation of the total lung surfa respectively Trace lesions were recorded but not score The total lung-lesion score of each group of mice is expresse as a percentage of the total possible

Experimental

Before ascribing the protective potency of norma horse serum used in this investigation to its γ-inhibitor component it was necessary to exclude the presence o antibody to Asian-type influenza viruses For this reaso it was tested in parallel with normal and immune rabbi sera for hæmagglutination inhibition against inhibito sensitive and resistant variants of the A/Singapore strain Rabbit sera were treated with crude R D E in an attemp to free them from non-specific inhibitors and wer absorbed with chorioallantoic membrane to remov antibody to the host-tissue component (Smith et al 1955) In addition, all the sera were tested before and after treatment with periodate, which is known to inactivate γ-inhibitor (Shimojo et al 1958) The results of these experiments are summarised in table I They show that γ-inhibitor in horse as well as rabbit serum can be clearly differentiated from specific antibody by its inactivity against the inhibitor-resistant variant, which is fully sensitive to antibody That the inhibitory activity of horse serum was not due to specific antibody is further evident from the complete inactivation of horse-serum inhibitor by periodate compared with only partial reduction of the activity of immune serum It was concluded that the horse serum used in the mouse-protection tests was free from specific antibody to Asian-type influenza viruses

TABLE I—HÆMAGGLUTINATION-INHIBITION TITRES OF INHIBITOR SENSITIVE AND RESISTANT VARIANTS WITH NORMAL AND IMMUNE SERA

Virus	Normal horse serum		Normal rabbit serum			Immune rabbit serum	
	Untreated	Periodate treated	Inactivated •	R D E. and C.A.M treated	R.D E, C.A.M, and periodate treated	R.D E. and C.A.M treated	R.D.E., C.A.M. and periodate treated
Inhibitor sensitive	>20,180	<80	248	174	<80	6246	1395
Inhibitor resistant	<80	<60	<80	<80	<80	6912	1555

• Inactivated at 53°C for 30 minutes

TABLE II—COMPARISON OF PROTECTIVE EFFECT OF INTRAVENOUS AND INTRANASAL HORSE SERUM

Serum admin 30 min before virus challenge		Serum admin. 30 min after virus challenge		Controls (serum only)		Challenge dose (L.D $_{50}$/0 05 ml.)
Intravenous	Intranasal	Intravenous	Intranasal	Intravenous	Intranasal	
10/10	0/6	5/5	1/6	0/6	0/6	$10^{2 \cdot 4}$ L.D $_{50}$

Numerator = no of deaths in 10-day observation period
Denominator = no of mice in group

Mouse Protection Tests

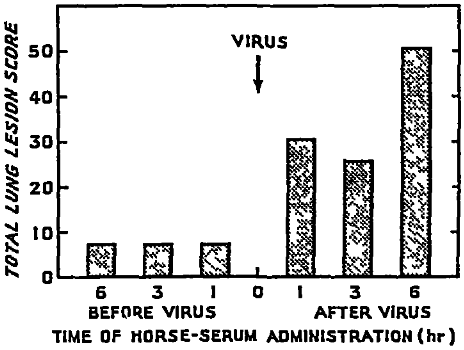
The protective effect of neat horse serum administered by the intravenous and intranasal routes was first compared Ten mice were inoculated with 0 25 ml of horse serum intravenously and six with 0 05 ml intranasally After an interval of 30 minutes both groups were challenged by the intranasal administration of 0 05 ml of seed virus diluted to contain an estimated dose of 10^2 L.D $_{50}$ In the same experiment twelve mice were inoculated with the same challenge dose, followed after 30 minutes by intranasal administration of 0 05 ml of horse serum into six of them and intravenous injection of 0 25 ml into the remaining six Two groups of six mice received intravenous or intranasal horse serum only One mouse, which died from non-specific causes without showing any typical influenza lung lesions, was excluded from the series The results summarised in table II show that intravenous administration of horse serum 30 minutes either before or after the virus challenge was extremely effective in protecting mice against death The serum given intravenously did not reduce the mortality-rate, but mice so treated survived somewhat longer than mice infected with one-tenth the challenge dose This delay effect was not investigated further The relative inefficacy of horse serum by the intravenous route is probably due largely to dilution of the inhibitor material in the circulation Very large doses of serum would have to be given systemically to achieve the required concentration in the lung tissues This is borne out by the observations of Henle et al (1941) on the passive immunisation of mice against influenza with immune serum These workers found that, to confer protection, about 5-10 times more serum was necessary by the intravenous than by the intranasal route

Further experiments were performed to determine the duration of the protective effect of intranasally administered horse serum 0 05 ml of horse serum was administered intranasally to each of thirty mice, and successive groups of six were challenged with an estimated virus dose of 10^2 L D $_{50}$ after 1, 3, 6, 24, and 48 hours Similarly thirty mice received the challenge dose first and successive groups of six were then given 0 05 ml of horse serum intranasally after the same time-intervals Bovine serum given 1, 3, and 6 hours before virus was also tested, and four mice received bovine serum only The actual challenge doses of virus used at different times during the experiment were obtained by infectivity titrations in mice and did not differ significantly from the estimated dose Six mice died from non-specific causes without showing any typical influenza lung lesions, these were excluded The results summarised in table III show that horse serum administered intranasally up to 48 hours before the virus challenge was strikingly effective in protecting mice against death Given up to 6 hours after the virus challenge it was almost equally effective, but after 24 hours was completely ineffective The absence of any protective effect with bovine serum, which does not contain any γ-inhibitor, confirms that the protective effect of horse serum is mediated by the γ-inhibitor The total lung-lesion scores of the various groups of mice treated with horse serum are shown in the accompanying figure From comparison of the scores for the 1, 3, and 6 hour groups, in which only one death occurred, it is evident that administration of serum before challenge was considerably more effective than administration after challenge Even with an interval of 6 hours between treatment and infection the lungs were much better protected than with treatment 1 hour after infection This is in accord with the protective effects of specific immune sera reported by other workers

TABLE III—EFFECT OF INTRANASAL HORSE AND BOVINE SERUM ADMINISTERED BEFORE OR AFTER VIRUS CHALLENGE

Horse serum										Bovine serum			
Time (hr) before virus challenge					Time (hr) after virus challenge					Time (hr) before virus challenge			Control serum only
1	3	6	24	48	1	3	6	24	48	1	3	6	
0/6	0/6	0/6	0/5	0/6	0/5	0/3	1/5	6/6	6/6	6/6	6/6	6/6	0/4

Numerator = number of deaths occurring during 10 day observation period.
Denominator = number of mice in group



Effect of horse serum on the total lung-lesion score

Discussion

Protection of mice against infection with an Asian influenza virus by the intranasal installation of normal horse serum has been demonstrated unequivocally, and there is little doubt that this is due to a serum component, which has been termed γ-inhibitor to distinguish it from the α and β hæmagglutination-inhibitors present in the sera of many animal species Virus neutralisation by specific antibodies is believed to depend on the blocking of virus receptor sites, essential for the initiation of infection, by the antibody molecules It is a reasonable assumption that the same mechanism underlies γ-inhibitor activity The greater efficacy of horse serum administered before the virus challenge supports this view The long duration of the protective effect suggests that the inhibitory material is of relatively large particle size which renders absorption into the circulation difficult Probably for the same reason the intravenous route of administration is less effective than the intranasal The protective effect of horse serum given up to 6 hours after the virus challenge is explicable on the basis of neutralisation of virus released from the early cycles of multiplication

The outcome of the investigation raises the question of the use of γ-inhibitor as a prophylactic and therapeutic agent in human influenza infections Smorodintseff and others have reported significant protection from infection by intranasal administration of hyperimmune serum in man (Smorodintseff 1939, Smorodinzew et al. 1940, Zhdanov 1959), and there is no reason to suppose that similar results could not be obtained by the use of γ-inhibitor in outbreaks caused by inhibitor-sensitive virus strains. Strains isolated in the laboratory from clinical cases, however, differ in their sensitivity to γ-inhibitor, though it is not yet known how far such differences are the result of laboratory manipulation Furthermore it has been shown recently that virus populations sensitive to γ-inhibitor may be heterogeneous and that inhibitor-resistant virus populations may be derived from them by passage in the presence of horse serum (Choppin and Tamm 1959, James and Fiset 1959, Cohen and Biddle 1960). A controlled trial of the prophylactic efficacy of horse serum during an epidemic, correlated with studies of the inhibitor sensitivities of freshly isolated virus strains, would yield valuable information.

An obvious clinical objection to the use of unrefined products of horse serum is the danger of serum-sensitivity reactions, although Smorodinzew et al (1940) did not observe any local or general reaction after intranasal administration of 2–3 ml. of immune horse serum in a series of 501 individuals receiving prophylactic inhalations. Moreover horse-serum fractionation, with a view to the concentration and partial purification of the γ-inhibitor, should reduce this risk as well as increasing prophylactic and therapeutic potency.

Apart from any immediate possibility of the practical use of γ-inhibitor, the demonstration that a virus-receptor-blocking agent, available in large quantity from a natural source, can alter the course of influenza infection of mice has important implications It is unlikely that γ-inhibitor is the only naturally occurring substance with such properties Indeed, a mucopolysaccharide, isolated from adult mouse intestine, was shown by Mandel and Racker (1953) to be capable of inhibiting both hæmagglutination and infectivity of the GD VII strain of mouse-encephalomyelitis virus Further search for agents of this type is called for.

Summary

Normal horse serum administered intranasally protected mice from death when given up to 18 hours before or 6 hours after 10^4 I.D.$_{50}$ of an Asian virus strain sensitive to γ-inhibitor Intravenous administration of horse serum was of little value The possibilities of the use of γ-inhibitor as a prophylactic agent in man are discussed

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BLOOD-SUGAR IN INFANTS AFTER LACTOSE FEEDS

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Hartmann et al. (1953, 1954) stated that in infants having milk feeds as much as 40% of the total blood-sugar may be galactose. They also found that after large doses of galactose (1·75 g. per kg. body-weight) by mouth the rise in blood-sugar may be entirely due to galactose, the glucose level sometimes falling and then rising again as the galactose falls. A similar effect was noted in infants who had had milk after a period of starvation or non-milk feeding for diarrhœa. To distinguish between glucose and galactose these workers used the "true" glucose estimation method of Somogyi, before and after yeast fermentation

With a glucose-oxidase and a copper-reduction method, Dormandy et al (1959) reached similar conclusions Studying two full-term and seven premature infants, they found that after a milk feed the difference between the total blood-sugar and the blood-glucose was as high as 60–80 mg. per 100 ml., and they assumed that the difference was due to the presence of galactose in the blood In two premature jaundiced infants they found a fall in blood-glucose after a milk feed, but repeated tests during the first few weeks of life showed a reversal of this phenomenon.

Recent work has suggested that the conclusions of these workers may be incorrect. By paper chromatography no galactose was demonstrated in the blood of newborn babies after lactose-containing feeds, although the frequent finding of galactose in the urine of these babies suggested that undetectable amounts must have been present (Haworth 1960) Sadoff and Ulstrom (1959) also found no galactose in the blood of newborn babies after milk feeds.

In this paper we describe further observations on the blood-sugar of infants after lactose-containing feeds.

Patients and Methods

Twelve babies were studied

Cases 1–8 were newborn babies (five premature and three mature) born at the Winnipeg General Hospital All were initially healthy, but one premature baby (case 2) later had a minor staphylococcal infection Cases 9–12 were inpatients at the Winnipeg Children's Hospital Case 9 was a baby aged 6 weeks, who was being treated for eczema but was otherwise healthy Case 10 had chronic diarrhœa of unknown cause, at the age of $2^1/_2$ months he was grossly wasted, and for several days before the test he had been having an artificial feed of strained meat, corn oil, and sucrose Case 11, aged 4 months, was recovering from gastroenteritis caused by a pathogenic strain of *Escherichia coli* He had been treated with intravenous fluids and starvation, feedings of diluted skimmed milk had been started the day before the test Case 12, aged 13 days, was under observation for hyperbilirubinæmia of uncertain cause (probably severe "physiological" jaundice)

The tests were conducted at the babies' normal feeding times—i.e., 4 hours or, for the smaller premature babies 3 hours after their previous feedings After the fasting blood specimens had been taken the babies were fed Six babies were given lactose dissolved in water, one was given galactose in water, and the remaining five were given a milk feed. The smallest premature babies were fed by stomach tube No baby vomited After the feed, which never took longer than 8 minutes, further blood samples were taken after 5, 15, 30, 60, 120, and, in a few cases, 180 minutes

Blood was collected by heel prick into dry heparinised capillary tubes After centrifuging, all samples of plasma were analysed for total sugar and glucose Except for the 5-minute samples, they were all chromatographed.

Total sugar was estimated by the method of King (1951) * Glucose was estimated by the glucose-oxidase method described by Huggett and Nixon (1957) A slight modification was adopted in that 2 ml of the glucose-oxidase reagent and 0 2 ml of the plasma filtrate were used, and, because this gave rise to some precipitation at pH 7, the reaction was adjusted to pH 6 Glucose standards and a blank were included with each set of estimations

Our chromatographic technique was a modification of the method originally used by Williams (1954) The silver-nitrate developer was that described by Trevelyan et al (1950) Initially the plasma was deproteinised for chromatography by taking 50 µl into a capillary tube, followed by an equal volume of 25% trichloroacetic acid The tube was sealed and centrifuged 50 µl of the supernatant protein-free fluid was then applied directly to the filterpaper By this method it was possible to detect 0 001% of galactose or glucose in the aqueous standard solution, but, because of interference from inorganic ions, it was not possible to detect less than 0 02% of galactose in the plasma For this reason the plasma from cases 10–12 was deproteinised by acetone 100 µl of acetone was taken into a capillary tube followed by 50 µl of plasma, and the procedure outlined above was then adopted By this technique there was less ionic interference, and galactose could be detected in a concentration of 0 01% in the plasma

Results

The results of the blood-glucose and blood-sugar analyses are shown in the table

Three tests were performed on case 2 because of the abnormal results from the first two tests When this premature baby was first tested at the age of 6 days, the blood-glucose 4 hours after the previous feed was nil by the total-sugar method, and only 2 mg per 100 ml by the glucose-oxidase method, and no trace of glucose was detected by chromatography Despite this the baby seemed to be in no distress, and showed no signs of hypoglycæmia After a dose of 3 g of lactose the blood-sugar rose slowly, and was still rising after 2 hours When the baby was retested at the age of 20 days profound hypoglycæmia was still evident, a more normal curve was obtained although the blood-sugar level was still abnormally high after 2 hours, but a 3-hour sample was normal. This baby had a minor staphylococcal infection at the time of the second test, and was being treated with erythromycin At 38 days of age retesting showed a normal blood-sugar response, although the fasting level was still slightly low

Case 1, a small mature day-old baby, also had no glucose in his blood 4 hours after feeding, and was without signs of hypoglycæmia After being given galactose 1 75 g per kg body-weight, the blood-glucose and total-sugar rose slowly to 46 and 50 mg per 100 ml respectively, and started to fall after 2 hours In case 7 the fasting blood-glucose level was 9 mg per 100 ml, and the total sugar was 22 mg per 100 ml Milder degrees of fasting hypoglycæmia were noted in the other newborn babies Case 10, the baby with chronic diarrhœa and wasting, showed a slow rise in blood-sugar, and there was no fall at the end of 2 hours Case 11, recovering from gastroenteritis, showed almost no rise in blood-sugar after a feed of 3 oz of milk. Histograms of the total-blood-sugar and blood-glucose levels of these cases are shown in figs 1 and 2

Case 12, the jaundiced baby, showed a mild fasting hypoglycæmia and a flat curve after 2¹/₂ oz of powdered milk.

Chromatography was not performed on the blood samples from case 1 because the volumes were inadequate, but in none of the other babies was galactose or any identifiable sugar, other than glucose, found In many of the blood samples, however, an unidentified reducing substance was found This was shown as a rather broad band on the filterpaper, below the position of the lactose. This substance was found as often in those blood samples which showed no difference between the glucose-oxidase and total-reducing-sugar methods as in those which showed a substantial difference, and it was present in several fasting specimens

Discussion

The table shows that in many of the blood samples examined the values obtained by the total-blood-sugar and the glucose-oxidase methods were appreciably different Minor differences might be accounted for by errors of technique, and this is likely to explain the eleven

TOTAL-BLOOD-SUGAR AND BLOOD-GLUCOSE LEVELS IN 12 INFANTS AFTER SUGAR FEEDS

Case	Sex	Age	Weight (lb & oz.)	Feed	Sugar (mg per 100 ml.)	Time (min) Fasting	5	15	30	60	120	180	Remarks
1	M	1 day	5 11	4 5 g galactose	Total sugar	0	15	26	48	50	44		Normal full-term
					Glucose	0	22	32	44	46	44		
(a)	M	6 days	2 11	3 g lactose	Total sugar	0	14	45	59	97	140		Normal premature
					Glucose	2	8	20	37	72	128		
(b)		20 days	2 10	3 g lactose	Total sugar	8	51	87	117	146	114	59	Mild staphylococcal infection
					Glucose	2	37	75	95	136	122	46	
(c)		38 days	3 15	3 g lactose	Total sugar	30	64	100	122	112	69		Recovered from infection
					Glucose	29	61	94	110	109	69		
3	F	6 days	4 0	5 g lactose	Total sugar	41	41	81	90	80	69	72	Normal premature
					Glucose	41	48	71	82	85	66	66	
4	M	5 days	3 10	5 g lactose	Total sugar	34	70	92		137	120	76	Normal premature
					Glucose	32	70	94	108	134	120	65	
5	F	3 days	6 15	3 g lactose	Total sugar	28	58	65	77	68	71		Normal full-term
					Glucose	10	30	34	58	49	56		
6	M	5 days	7 2	2¹/₂ oz. evaporated milk=3 g lactose, 1 g sucrose	Total sugar	35	69	105	107	73	63		Normal full-term
					Glucose	35	61	84	92	58	49		
												155	
7	F	4 days	3 12	25 ml evaporated milk=0 7 g lactose, 0 6 g. sucrose	Total sugar	22	58	88	105		48	59	Normal premature
					Glucose	9	44	75	78	51	35	42	
8	M	6 days	3 8	3 g lactose	Total sugar	39	53	73	76	96	64		Normal premature
					Glucose	30	52	66	80	111	66		
9	F	42 days	8 12	3 g lactose	Total sugar	88	117	119	130	111	80		Eczema
					Glucose	77	100	109	110	93	70		
	M	2¹/₂mos	6 6	3 oz. evaporated milk=4 3 g lactose	Total sugar	45	49	52	60	61	73		Diarrhœa, wasting
					Glucose	40	47	47	54	50	62		
	F	4 mos	11 2	3 oz. milk=4 g lactose	Total sugar	79	84	83	83	92	87		*Esch coli* enteritis
					Glucose	74	74	75	78	84	74		
12	M	13 days	6 4	70 ml powdered milk=4 9 g lactose	Total sugar	35	49	64	91	64	61		Jaundice (bilirubin 13 9 mg per 100 ml)
					Glucose	32	42	61	92	78	64		

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* We have found that this method measures 100% glucose, 85% fructose, 68% galactose, and 28% lactose

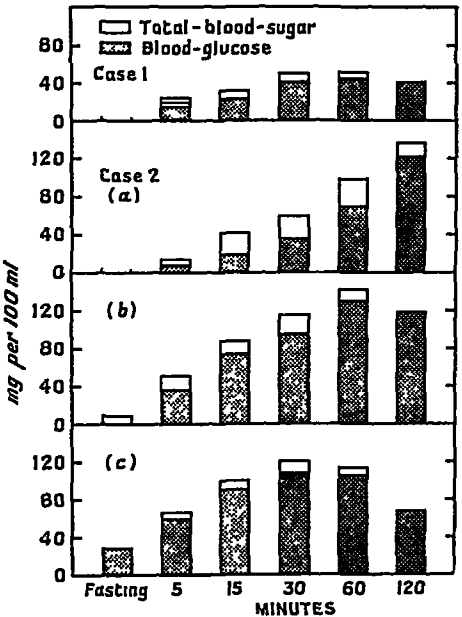

Fig 1

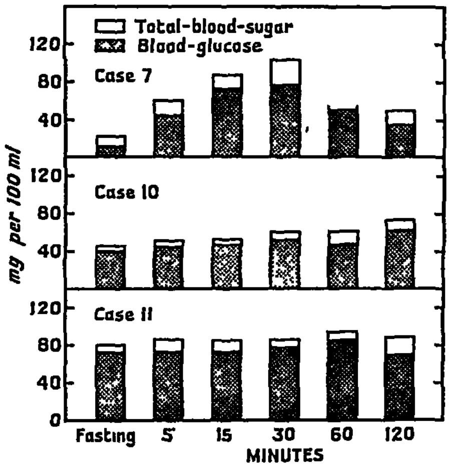

Fig 2

Fig 1—Total-blood-sugar and blood-glucose levels in case 1 after a feed of 4 5 g galactose, and in case 2 after three feeds of 3 g lactose

Fig 2—Total-blood-sugar and blood-glucose levels in cases 7, 10, and 11 after feeds of milk and lactose

instances in which the glucose-oxidase method gave slightly higher readings than the total-sugar method In only three fasting specimens (from cases 5, 7, and 9) was the difference greater than 10 mg per 100 ml, but in twenty-nine of the samples after feeding a difference of more than 10 mg was found, and in eight it was greater than 20 mg In the 15-minute sample from case 5 a difference of 31 mg per 100 ml was observed It has been suggested that blood "saccharoids" are responsible for the non-glucose fraction in blood, and their significance has recently been discussed by Middleton (1959)

Galactose was not identified by chromatography in any of the blood samples from the eleven babies after 13 lactose feeds This confirms our previous findings (Haworth 1960) Taking into account the limits of sensitivity of the chromatographic method, one can therefore conclude that any galactose in the blood of cases 2–9 could only have been present in concentrations of less than 20 mg per 100 ml, and in cases 10–12 in concentrations less than 10 mg Therefore in those samples of blood from cases 2–9 showing a saccharoid fraction above 20 mg per 100 ml, the fraction was not entirely due to galactose, and the same conclusion holds for samples from cases 10–12 showing a fraction greater than 10 mg Small amounts of lactose and galactose must be present in the systemic blood after lactose feeds because these sugars are often found in the urine, but the concentration must be usually less than 1 mg per 100 ml because the total amounts of these non-threshold substances excreted are very small (Haworth 1960) Lactose and galactose in larger amounts have been demonstrated occasionally by chromatography in the blood of babies after ingestion of lactose (Haworth and MacDonald 1957, Haworth 1960)

The unknown substance found by chromatography may be related to the saccharoid fraction, although no obvious correlation was observed in the difference between the two methods of blood-sugar analysis and the filter-paper stain Further work is in progress to clarify this point

These conclusions conflict with the statements of Hartmann et al. (1953) and Dormandy et al (1959) that galactose formed a high proportion of the total blood-sugar of infants after milk feeds But these workers only suggested the likelihood that the difference between the total-sugar and glucose in the blood which they examined was galactose Sadoff and Ulstrom (1959), who conducted tests similar to ours, demonstrated no galactose (above 3 mg per 100 ml) in the blood of infants after milk feeds They also showed no statistical difference between the results of their total-sugar and glucose methods, but the sugar content in individual samples of blood varied so much that their technical methods must be suspect

In none of our cases did the blood-glucose level fall after lactose was given, and we were therefore unable to confirm the observations of Hartmann et al (1953, 1954) and Dormandy et al (1959) The seven "premature" babies which Dormandy et al studied all apparently weighed over 6 lb, and would not, therefore, be considered premature by the usually accepted standards

It was remarkable that in two babies (cases 1 and 2) we could demonstrate no sugar in the blood 4 hours after feeding These babies were in no way distressed, and showed no signs of hypoglycæmia Lesser degrees of fasting hypoglycæmia were found in the other newborn infants Hypoglycæmia in the newborn period is well recognised, being more pronounced in premature babies (Hartmann and Jaudon 1937, Miller and Ross 1940, Norval et al 1949, Norval 1950, Farquhar 1954), and many workers have commented upon the frequent lack of symptoms attributable to it The cause is unknown, although Farquhar (1954) discussed some of the possibilities It may be related to the apparent lack of secretion of adrenaline by the infantile adrenal medulla (Greenberg and Gardner 1959)

The hypoglycæmia seen in cases 1 and 2 was more profound than that reported by the above workers, and this raises questions as to what substances these babies were using for their metabolism The first dose of lactose given to the very immature baby (case 2) caused the blood-sugar and glucose to rise in a linear fashion from zero, and it was still rising 2 hours after the feed Later tests on this baby showed a more normal response, although fasting hypoglycæmia was still apparent at the age of 38 days Case 10 had a similar type of blood-sugar response, although this baby did not have a low fasting sugar level. The significance of the response in case 2 is unknown, but it may have been the result of either slower absorption or inefficient liver function, perhaps due to prematurity, although the rise in 5 minutes was comparable to that seen in the other babies

The capillary-tube method which we used for deproteinising the plasma for chromatography has not, we believe, previously been described We found it valuable when dealing with such small volumes because it entails a very slight loss of plasma

Summary

Total-blood-sugar and blood-glucose levels were estimated in eleven infants after lactose-containing feeds, and in one infant after a galactose feed. Three of the infants were normal full-term babies, five were premature, one was jaundiced, two had diarrhœa, and one had eczema. They were aged 1 day to 4 months.

After the feeds several samples of blood showed saccharoid material, amounting to 20–30 mg. per 100 ml., as deduced from differences in the two methods of analysis.

Galactose was not identified in any of the blood specimens examined by paper chromatography, and it was therefore concluded that this sugar was not present in amounts greater than 10–20 mg. per 100 ml., which could not account for the whole saccharoid function. These findings differ from those of previous workers who reported a high concentration of galactose in the blood of infants after the ingestion of lactose.

Fasting hypoglycæmia was found in all the newborn babies examined, and two had no detectable sugar in their blood. None of these babies showed any symptoms attributable to the hypoglycæmia.

We wish to thank Dr. H. Medovy, Dr. S. Israels, Dr. K. C. Finkel, and Miss B. Gourley for their advice and criticism, and several other physicians for permission to study their patients. This work was supported by a Mead Johnson grant for pædiatric research, administered by the American Academy of Pediatrics.

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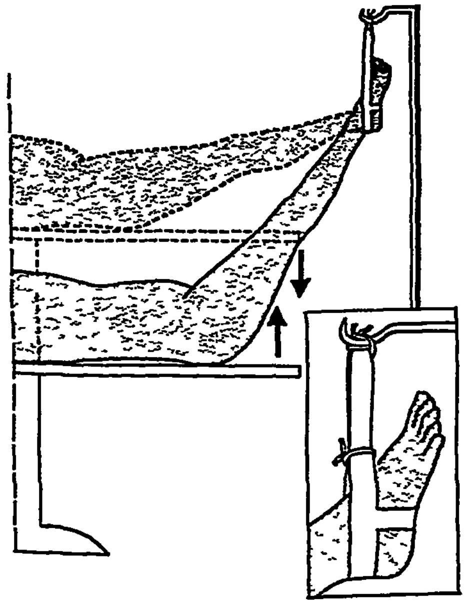
New Inventions

LIMB SUSPENSION IN VARICOSE-VEIN SURGERY

This method has been in use for some 10 years, but does not seem to be widely known. The advantages are that blood-loss is reduced almost to nothing, hæmatomas do not form, and access to the limb is so good that the patient seldom needs to be turned during operation. Skin preparation, towelling, and bandaging are also easier as no assistant is needed to hold up the leg.



Technique.—With the table low the limb is suspended almost vertically from a mobile stand by a webbing sling under the heel (see figure). The table is then raised to a convenient height, which opens the groin. When the groin dissection is complete, and the stripper has been inserted, the table is lowered. The vein is then stripped, and other interruptions are performed, with very little bleeding. The incisions are closed, and a 6-in. crêpe bandage is applied.

The illustration was drawn by the department of medical illustration, Guy's Hospital.

Guy's Hospital,
London, S.E.1

REX LAWRIE
M.D., M.S. Lond., F.R.C.S., M.R.C.P.

Reviews of Books

Prematurity

Diagnosis, Care and Disorders of the Premature Infant. BERYL CORNER, M.D., F.R.C.P., consultant pædiatrician, United Bristol Hospitals, and lecturer in child health, University of Bristol. London: Cassell. 1960. Pp. 600. 105*s*.

THIS fine new book on the important social, economic, and medical problem of prematurity is a tour-de-force by one very well qualified to write it. It deals with all aspects of prematurity and caters for all concerned—doctors, research-workers, students, midwives, nurses, and health visitors—and Dr. Corner rightly emphasises the importance of understanding the anatomy and physiology of such immature creatures by including an authoritative section of 130 pages on these aspects. There follows an excellent section of equal length on the care of the premature infant, the fruit of long practical experience by the pioneer of the fully comprehensive service for the care of all premature babies born in the Bristol area. The section on the disorders of the premature infant is also comprehensive and much of it also applies to the mature newborn infant, but it is salutary to consider all the ills of premature babies in the light of their frailty and special circumstances. This section includes a valuable chapter on disorders of the eyes by Mr. C. A. Brown, an ophthalmologist with much experience of the newborn. The final section is concerned with prognosis, both immediate and remote, and this includes a good account of the pathology of the premature infant by Dr. Norman J. Brown, who has collaborated with Dr. Corner for many years. There is an ample well-chosen bibliography and 139 good illustrations.

This balanced, pleasantly written book is certainly an essential for all concerned with the care of premature babies.

Pediatric Dermatology

HENRY H. PERLMAN, M.D., PHAR. D., clinical professor of pædiatrics, Jefferson Medical College, Philadelphia. Chicago: Year Book Publishers. London: Interscience Publishers. 1960. Pp. 477. 135*s*.

INCREASING demand for specialised textbooks has stimulated Dr. Perlman to write this excellent one designed for pædiatricians, general practitioners, teachers, and students. It had its beginning as long ago as 1928 in a series of lectures and demonstrations to graduate students at the Children's Hospital in Philadelphia.

The general reader will be glad that histopathological descriptions are kept to a minimum and he will welcome the detailed attention to differential diagnosis. A praiseworthy departure from textbook practice is the amount of space—50 pages—allotted to the principles of treatment, remedial agents, and the formulary Too few teachers emphasise, as Dr Perlman does, the importance of simplicity in treatment, the knowledge of the composition of preparations being prescribed, and the exact effect of each ingredient He also rightly stresses not only the necessity to avoid blunderbuss prescribing but also to choose the proper base or vehicle and the correct quantity, bearing in mind the age of the patient, the area involved, and the frequency of application Many students on qualification remain mystified about the basic composition of lotions, creams, and pastes and when one should be used in preference to another The answers to these questions are given clearly and in detail The formulary, easy to find, being on light blue paper, ends with a novel and useful section on the removal of stains from the skin and clothing the advice should be specially welcome to the patient with chronic psoriasis who has to contend with preparations containing tar and dithranol which often ruin his underwear and nightwear

There are some minor points of controversy Granuloma annulare has never been proved to be tuberculous and should not be included in the chapter on cutaneous tuberculosis, but rather with other allergic conditions British dermatologists would no longer approve of liquor arsenicalis in the treatment of this condition or of dermatitis herpetiformis, in view of the possible late development of squamous-celled carcinoma of the skin Dr Perlman rightly points out that cutaneous tuberculosis is far less common in the United States than in Europe, which in part excuses him for not being completely up to date with the latest therapy for lupus vulgaris, Bazin's disease, and tuberculosis verrucosa cutis It is now hard to justify, however, the use of radiotherapy in the latter two conditions Excision and diathermy have now been outmoded by chemotherapy in the treatment of verruca necrogenica

The quality of production is excellent, and the illustrations, all in black and white, are well chosen and of good definition The index is extensive and accurate, and a few well-chosen references are included at the end of each chapter

A Study of Abortion in Primitive Societies

GEORGE DEVEREUX London Thomas Yoseloff 1960 Pp 394 35*s*

IN his struggle to survive, both as an individual and as a member of an organised group, man has long been deeply concerned with laws and customs relating to abortion. Primitive societies with their high natural birth wastage were undoubtedly acutely sensitive to the artificial interruption of pregnancy, which might threaten the very survival of the tribe In this book Dr Devereux describes the circumstances of abortion in some 400 primitive, preindustrial societies In the light of an extensive examination of what has been written on the subject, he sets out the indications, the techniques employed and by whom, the individual and collective attitudes adopted towards it, and discusses the alternatives and possible physical and social consequences He also deals at some length with the role of sex in primitive societies An extensive bibliography will allow readers to consult the original works The book is of interest primarily to anthropologist and psychologist, but sociologist and gynæcologist will find in it many useful references

A Primer in Medicine

M H PAPPWORTH, M D, M R C P London Butterworth 1960 Pp 241 32*s* 6*d*

DESCRIBED as a "primer" although dealing only with the cardiovascular, respiratory, alimentary, and neurological systems, this book is based on the author's course for the M.R C.P and is primarily intended for students in their first clinical year They may find much of it hard to understand, and they will seldom appreciate what lies behind the repeated thrusts at modern medical practice, indeed, Dr Pappworth has allowed himself so much destructive criticism that the rest of his teaching seems less persuasive He is insistent that students must learn facts, as indeed they must, but most teachers find that the facts are better remembered if the underlying mechanisms are understood Unashamedly directed towards examination results, this book is unlikely to inspire the student or encourage the inquiring attitude needed to sustain his medical interest or powers of observation after qualification.

Margaret McMillan

The Children's Champion G A N LOWNDES, M C, B LITT, J P London Museum Press 1960 Pp 110 15*s*

1960 is the centenary of the birth of Margaret McMillan, pioneer in nursery-school education and in children's health and welfare. This book is the result of the Nursery School Association's decision to celebrate the centenary by asking a number of people who knew Margaret McMillan to write a personal appreciation of her Contributors include Viscountess Astor, Sir Cyril Burt, Arnold Gesell, Earl Russell, Dame Sybil Thorndike, and a number of Margaret McMillan's former colleagues, associates, and pupils The book includes chapters on her early years and personality, her pioneer work at Bradford, her work in London, the open-air nursery school, the Rachel McMillan Teachers' College at Deptford, the Margaret McMillan Memorial College at Bradford, and, finally, the McMillans' place in England's Silent Revolution and the Unfinished Task

When Margaret McMillan worked in Bradford in the 1890s about a third of all babies died in their first year When she opened her school at Deptford in 1911, 80% of the children had rickets Setting out to improve this deplorable state of affairs, she met violent opposition, and only a handful of people even understood what she was trying to do Disease, deformity, and death were accepted as the unavoidable lot of the children of the poor, even by the poor themselves

The book inevitably seems to be superficial in places, for it is, after all, a tribute rather than a profound study But it is of special interest because many different kinds of people have contributed to it and because it shows how many of the ideals for which Margaret McMillan fought have been achieved, and how many have not At present there is a nursery-school place available to about 1 child in 65 The book ends with the suggestion that the provision of more nursery schools might lessen the incidence of broken homes, mental ill-health, and crime

Christopher's Textbook of Surgery (7th ed Philadelphia and London W B Saunders 1960 Pp 1551 119*s*)—Since last we noted this work two editions have appeared and the editorship has passed from Dr Christopher himself to the next generation and the able hands of Dr Loyal Davis. Four years ago Dr Davis introduced a change of policy with the 6th edition he saw what all too few textbook authors and editors appreciate—that complete factual cover is no longer feasible or desirable, that the basic facts and principles of each subject well and coherently told will stimulate the student to seek further knowledge for himself in the library and at the bedside As a result the book is very readable and takes its place with the best textbooks of surgery in English language it is intelligently contrived, well executed, and as up to date as works by many authors can be

The Transparency of the Cornea (Oxford Blackwell Scientific Publications 1960 Pp 268 45*s*)—Following the 18th International Congress of Ophthalmology held in Brussels some participants met at Knokke-le-Zoute to discuss the complicated problem of transparency of the cornea The nineteen papers at this symposium, organised by the Council for International Organisations of Medical Sciences, ranged over anatomy and development of the cornea, pathological reactions, the biophysics, the biochemistry, and the metabolism of the cornea, and the deposition of fat and crystalline deposits Five of the papers dealt with different aspects of corneal grafting, and while each discipline could bring its quota of observations, it is clear that we are still a long way from understanding the rare physiological phenomena presented by transparency of tissues The various contributions brought little that was new, but the symposium and the proceedings, edited by Sir Stewart Duke-Elder and Mr E S Perkins, served a very useful purpose in bringing together a scattered literature.

THE LANCET

LONDON 8 OCTOBER 1960

Sport and Medicine

WHOEVER reads the summary of the new Wolfenden report[1] before the preceding 106 pages may find it rather dull There are no surprises in it, and evidently the committee have been at pains to consider everything and to offend nobody's susceptibilities—partly perhaps because there were nine members[2] rather than four or five who might have been more adventurous, but largely because of their terms of reference and the policy which governed their selection The terms of reference were "To examine the factors affecting the development of games, sports and outdoor activities in the United Kingdom and to make recommendations to the Central Council of Physical Recreation as to any practical measures which should be taken by statutory or voluntary bodies in order that these activities may play their full part in promoting the general welfare of the community" The members of the committee were selected, "on the basis of their ability to examine and assess evidence, as well as their general interest in the subject" Taking these things into account, *Sport and the Community* is a first-class review of the situation, and its recommendations are a logical corollary Unfortunately, there is nothing to suggest what the Central Council of Physical Recreation should do next The report has had a pretty good Press, which was no doubt the outcome of good timing and the choice of a public figure as chairman, as well as the obvious news value of sport And presumably this publicity is all that the Central Council set out to achieve, relying on the resulting public interest to exert the necessary pressures to action Even so, unless the Chancellor of the Exchequer has a deep personal interest in the subject, what can be expected to happen next—if anything?

A word that is conspicuously absent from the report is health, and, since the context embraces the promotion of the general welfare of the community, this is surprising One can understand the committee's reluctance to get knee-deep into the relation between health and exercise, but they might have had a try up to their ankles Health has long been defined in terms of what it is not, and there is much statistical evidence correlating ill health of one sort or another with sedentary habits Admittedly this does not prove that health and physical activity are inseparable, but as a profession we are on record as having advised the general public that regular physical activity is a preventive for, among other things, coronary thrombosis, and this advice applies equally to a number of chronic conditions But the report fights shy of this aspect

The committee mention the encouragement of medical matters relating to sport, in particular "advances in methods of training and technique" But instead of sweeping the argument firmly along by way of the help such advances could give in reducing the incidence of sports injuries, they refer only to "reducing the amount of time lost in industry and school by sports injuries" Another paragraph suggests that the proposed Sports Development Council, which would be primarily concerned with finance, should also assume responsibility for the coordination of the relevant researches of the British Association of Sport and Medicine, the consultant medical panel of the Central Council of Physical Recreation, the Ergonomics Society, certain branches of the Medical Research Council, and the medical officers of the governing bodies of sport This seems to ask too much of a lay committee assembled to spend an annual £5 million on sport By all means let these efforts be coordinated, but it will take some firm handling and a very clear idea of what is wanted

The need to improve the treatment of sports injuries is plain, but that is only a beginning There is an enormous opportunity for research in sport and medicine The most pressing problem is the extent to which the physical efficiency of the locomotor system influences the efficiency of other systems There are two reasons why it is important First, the general public has more leisure time than ever before, and it is going to have to find ways of occupying an increasing proportion of leisure time over an indefinite period Both the demand for facilities for physical activities and the incentives for taking part in them are certain to increase Equally certainly there will be a demand for increased medical understanding of physical activity, not merely from the viewpoint of the consequent injuries but also in the various aspects of social medicine Secondly, there is a definite connection between the performance of the healthy human body under stress and that of the ill-healthy one trying to live a normal life, and the inferences to be drawn in this way can be applied to every system in the body In athletic performance there are relevant mechanical factors, but we know little about them, and almost nothing of the way in which a mechanical factor affects performance For instance, if an athlete's chest expansion is 3 in. when the expected normal for his physique is 4, is his performance affected by lack of air or is the excessive use of the accessory muscles of respiration interfering mechanically with the action of other muscles, and so forth? If an athlete's circulorespiratory system is the limiting factor in his performance, can the techniques to alleviate strain on this system be applied, say, to the treatment of a chronic bronchitic who is apt to go into cardiac failure? There is in fact no limit to the range of [illegible] into this sort of thing, and much might be [illegible] aetiology of many diseases "The sooner [illegible] to it, and learn the extent to which our [illegible] on the mechanical and functional effi[illegible] the better "[3] In this exciting territory of medical research it is unlikely that the proposed Sports Development Council would be the proper coordinating authority—but they might give very welcome financial help

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[1] Sport and The Community Report of the Wolfenden Committee on Sport, 1960 London Central Council of Physical Recreation. Pp. 135 3s 6d.

[2] Sir John Wolfenden, Mrs G C Allen, The Bishop of Chester, Miss E B Clarke, Sir Godfrey Ince, Mr J L Longland, Mr A D Munrow, Mr H A Pawson, and Sir Arthur Porritt, P R.C.S

Virus Infections During Pregnancy

It is nearly twenty years since Gregg,[4] in Sydney, Australia, noted that the mothers of a group of children with unusual congenital cataracts often gave a history of german measles in the early months of the pregnancy The cataract was often associated with a congenital malformation of the heart, and the children tended to be small and difficult to feed There had been an epidemic of rubella in Australia the year before, in which a higher proportion of patients were seriously ill than is usual with rubella Later studies in New South Wales,[5] and in South Australia[6] established that the infections really were rubella, that congenital deafness might be caused in the same way, that there was no relation between the severity of the maternal infection and the nature of the defect in the child, that only infection during the first three months of pregnancy was likely to produce malformation, and that the timing of the rubella was related to the nature of the defect, heart and eye defects more often following rubella in the first two months, and deafness more often following rubella in the third month of pregnancy

Many studies have been reported since, a notable one being that by Clayton-Jones[7] on the frequency with which the mothers of deaf children in this country had had rubella in pregnancy Most of these studies were retrospective This approach was well suited to the discovery of the types of defect that might be caused by rubella in pregnancy, but would not answer the important question how often such an illness was followed by malformation Swan and his colleagues[6] had estimated that the risk was nearly 100% if the illness occurred in the first two months, and 50% if it occurred in the third month Swan,[8] and also, with more circumspection some American authorities,[9] were still citing high risks in 1949 It was obvious to those with experience of the pitfalls of retrospective inquiries that such estimates were unreliable What was needed was studies in which rubella in pregnancy was ascertained independently of the outcome of the pregnancy, and subsequently the children resulting from the pregnancy were carefully examined The first of these prospective studies had already been reported in 1946 Fox and Bortin,[10] in Milwaukee, found only 1 malformed child in 9 instances where rubella had occurred in the first four months of pregnancy Several such studies have appeared since Hill and his colleagues, combining four such studies, including one of their own[11–14] estimated that the risk following rubella might be as high as 50% in the first month, 25% for the second month, 17% for the third, and probably not increased above the random risk when the infection occurred later than this Only one prospective study[15] has suggested appreciably higher risks, and several studies, including one that was retrospective, have suggested lower risks

Clearly there was need for a much larger prospective study, and in 1950 one such study was begun in England and Wales and later in Scotland[16] This was planned by the Ministry of Health and the General Register Office, and executed by the medical officers of health in their own areas

The study was continued for two years From women under antenatal supervision, two groups were selected " virus infection cases " who, on coming under observation, had already had a virus infection during their pregnancy, or subsequently developed an infection during the pregnancy, and " controls ", who had not had a virus infection during the pregnancy on coming under observation, or later during the pregnancy, and whose birthdays were on the 31st of the month—a random 2% sample Any control who developed a virus infection after coming under observation was transferred to the " virus infection " group The virus infections included were rubella, measles, mumps, chickenpox, and poliomyelitis The subsequent procedure in the words of the report was as follows

> " After selection, virus and control cases were kept under observation until the termination of the pregnancy In the event of abortion, miscarriage or still birth the record card was completed as far as possible and returned to the General Register Office In the case of live births the children were kept under observation for two years, medical examinations being undertaken as soon after birth as possible, at one year and at two years of age by local health authority or hospital medical officers or by the family doctor After the third medical examination or on the death of the child before 2 years of age, the completed record card was returned to the General Register Office "

By the end of 1952, 1745 virus infection cases and 6619 controls had been registered with the General Register Office, and these, after various losses, left 1513 cases and 5717 controls The " virus infection " cases included 578 of rubella, 103 of measles, 298 of chickenpox, 501 of mumps, and 33 of poliomyelitis There was a rubella epidemic in 1952 and the majority of rubella cases were ascertained between February and November that year In the winter of 1950–51 there was an epidemic of virus influenza, and the opportunity was taken to register instances of virus influenza in pregnancy for eight weeks in Liverpool and Manchester, producing 161 cases, 12 of which occurred in the first three months of pregnancy

The main interest of the report lies in the end results of the 578 rubella cases In 376 mothers the rubella occurred after the twelfth week of pregnancy, in this late group the percentages of abortions, of stillbirths, and of deaths before the age of 2 years were essentially similar to those in the control group But in the 202 instances where rubella had occurred in the first twelve weeks of pregnancy, all the percentages were raised compared with the control groups—5 0 compared with 2 4 for abortions (therapeutic abortions were excluded), 4 5 compared with 2 4 for stillbirths, and 6 9 compared with 2 4 for deaths under the age of 2 years In this early rubella group, the percentage of children alive at the end of two years was 83 6, compared with 92 8 of the controls. This 83·6% included, however, 13% with major malformations, compared with only 1·5% among 2-year-old survivors in the control group. Thus, the figure that may be most useful in practice is that, of 100 women who experienced rubella in the first twelve weeks of the pregnancy, 73 (just under three-quarters) had a child alive and without apparent major malformation at the age of 2 years (though about 1 in 8 of these would later be found to be partially deaf). For 100 women in this group who had a live-born child, 80 would have a child alive and not malformed at the age of 2 years. For the control women, the corresponding figures were 91 and 96.

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[3] Troup, J D G *Lancet*, Sept 24, 1960, p 699

[4] Gregg N M *Trans ophthal Soc Aust* 1941, 3, 35

[5] *Med J Aust* 1945, ii, 122.

[6] Swan, C, Tostevin, A. L., Moore, B, Mayo, H., Black, G H. B *ibid* 1943, ii 201

[7] Clayton-Jones E *Lancet*, 1947, i 56

[8] Swan, C *J Obstet Gynæc Brit Emp* 1949 56 341, 591

[9] Wesselhoeft C. *New Engl J Med* 1949, 240, 258

[10] Fox, M J, Bortin, M M *J Amer med Ass* 1946, 130, 568

[11] Brown, C M, Nathan, B J *Lancet*, 1954, i 975

[12] Brawner D L. *J med Ass Ga*, 1955 44, 451

[13] Pitt D B *Med J Aust* 1957, i, 233

[14] Hill, A B, Doll, R., Galloway, T McL., Hughes, J W P *Brit J prev soc Med* 1958, 12, 1

[15] Lamy M, Seror, M E. *Bull Acad nat Méd, Paris*, 1956 140, 196

[16] Rubella and Other Virus Infections During Pregnancy *Rep publ Hlth med Subj, Lond* no 101 H M. Stationery Office 1960 Pp 101 7s

As regards more detailed findings of the malformations among the early rubella cases, there were 6 therapeutic abortions, and in the 2 of these where the fœtus was examined it was apparently normal. Information about the cause of the 9 stillbirths is incomplete, but there was 1 case of congenital heart-disease. Of the 14 deaths before the age of 2 years, 4 were associated with malformation and prematurity, 2 with malformation alone, and 3 with prematurity alone. So the association of early rubella with malformation, and also with prematurity (by weight rather than gestation-time), accounted for the high infant mortality. The total major-malformation rates for liveborn children, estimated at the age of 2 years, were 2·3% for the control group, 2·2% where the rubella occurred after the twelfth week, but 15·8% for rubella in the first twelve weeks. The figures for the thirteenth to sixteenth week —4·2%—suggest that the period of risk extends a little beyond the twelfth week. The incidence among live births of individual malformations when the rubella occurred in the first twelve weeks was congenital heart-disease 7·1% (0·5% in the controls), cataract 5·5% (0·04%), congenital heart-disease and cataract 3·3% (none in the controls), deafness and suspected deafness 6·0% (0·4%), mental defect 1·6% (0·4%). No other malformations occurred with significantly increased frequency in the rubella group. The major-malformation rate for live-born children, related to the month of onset, was 15·6% up to the fourth week, 19·7% for the fifth to eighth week, and 13·0% for the ninth to twelfth week.

Later examination of 237 of the rubella children at the ages of 3 to 7 years showed that many instances of deafness, and a few of mental retardation, but none of other major malformations, had been missed. The total incidence, including milder cases, of congenital perceptive deafness was 19% for rubella in the first twelve weeks, and was still 12% for the thirteenth to sixteenth week. This emphasises the importance of early expert examination of the hearing of children, born after rubella in the first four months of pregnancy, so that those who are deaf may not be left dumb and educationally retarded.

The findings on the other virus infections may be briefly summarised. As in earlier surveys, there was no clear evidence that any of them harmed the fœtus. There was a rather high incidence of malformation after measles, but neither the timing nor the type of malformation suggest a strong association with the measles infection. The series of poliomyelitis cases was too small for satisfactory comparison with the controls, but indicated a risk of fœtal death rather than malformation.

All those concerned are to be congratulated on this admirably planned and executed study. It is incomplete in only one respect. The later examinations did not include formal intelligence tests. These might well be done now that the children are aged 7–9 years, in order to see whether, if the tests are suitably modified for those who are deaf and those who are severely mentally retarded are excluded, there is any evidence of minor degrees of mental retardation in the early rubella group. Many parents would be more concerned at the risk of having a dull child than of having a deaf child.

Annotations

THE SPACE AGE

At the Institute of Biology's symposium on the Biology of Space Travel, held in London on Sept. 29 and 30, a note of exasperation and disapproval was sometimes detectable—the exasperation of a man forced to shift his attention from his familiar microscope to a telescope; the disapproval of a partisan who, short of funds for his special interest, sees money diverted to a project he considers frivolous. This attitude of reaction is natural, and it is one that has often opposed exploration in the past, but it contrasted ill with the spirit of the pioneers whose names adorn the walls of the Royal Geographical Society's lecture hall, where the symposium was held.

It seems to be generally accepted, even by those who disapprove, that there are no insuperable biological difficulties to prevent a man circumnavigating the earth in a low orbit; many believed that Mr Khruschev might celebrate his visit to the United Nations Assembly by announcing the success of the first Russian astronaut. Long journeys and actual human contact with other planets are quite another matter. Even at the present precipitate rate of advance, space travel of this sort is some way off, for the difficulties, both biological and technological, are formidable.

There is no obvious solution to the problem of nutrition during a lengthy journey. When every pound weight hoisted into space takes one thousand pounds of thrust, normal victuals to keep a man alive for a year are out of the question. There has been much work on dehydrated foods, which, when reconstituted, are now said to provide a diet normal in taste, texture, and even appearance, on closed biological cycles to re-use the body's waste, and on algal concentrations which, by photosynthesis, do the threefold office of carbon-dioxide absorption, oxygen generation, and food production. But none is entirely suitable, and revolutionary alternatives were discussed.

A body in suspended animation needs no food. The achievements of hypothermia in surgery led some speakers to wonder whether an astronaut could not be reduced to a piece of anabiotic cargo for the greater part of the journey, but the justification for exposing a man to the hazards of space flight is that he has the powers of observation, reasoning, and decision which are needed to ensure or exploit success. The experience of the doctors supervising the first American manned space project is that the astronaut, who was first accepted by the engineers on sufferance, has been asked to monitor and control so many of the satellite's systems that he has become the most active cog in the whole complex machine As Dr Grey Walter pointed out to the conference, the human brain is a computor which, in terms of volume, weight, power requirement, cost, and versatility, is unlikely to be rivalled by any electronic assembly for a very long time

A more fundamental idea was advanced by Mr N W Pirie, who noted that much of the metabolic work of the cell is concerned with the phosphorylation or reduction of a few intermediate molecules It might be possible to restore these molecules to the resting or potential energy state by some external means Such an attractive method of recharging the human battery would have many applications besides that of space flight, especially in a world in danger of overpopulation and starvation

Unfamiliar microorganisms may exist on other planets, and if these were brought back to earth by careless astronauts the consequence might be grave But for the next year or so the danger is rather in the opposite direction Our own bacteria, if they were transplanted, might soon become so dominant that indigenous life of all sorts would be destroyed or so modified that priceless biological evidence on the origins of life would perish for ever This is the danger of rockets fired to collide with our neighbours in the heavens, but it is a danger which, now that it is understood, can be averted The Russian moon probe is said to have been decontaminated by the time it left our atmosphere, but whether absolute decontamination is possible with present techniques is open to question Large-scale sterilisation needs examination if the fate of the Martians in Wells' *War of the Worlds* is not to have disastrous parallels on earth or on other planets

The sciences of biology and astronomy are likely to derive the greatest benefit from space research, though not all astronomers are free from the reluctance noted at this biological symposium One celebrated astronomer who has no doubts about the value of space flight is Dr Harlow Shapley, of Harvard Observatory, who confessed himself converted to the view that the space programme was among the three most important pieces of current research, principally because of the rich byproducts to be expected of it Whatever our personal estimates of the various research priorities, we must accept the fact that the space age has begun, that there are biological and medical implications of the greatest importance to the human race, and that we must see that these implications are understood and planned for

ESSENTIAL HÆMATURIA

THE appearance of blood in the urine is sometimes the first evidence of malignant disease of the bladder or kidney, of a stone, or of an inflammatory lesion With modern methods of investigation the cause of bleeding can be localised and defined in most cases, but in a few no satisfactory explanation is found The term " essential renal hæmaturia " is applied to cases in which definite and often serious and repeated unilateral bleeding takes place in the absence of demonstrable morphological changes in the renal tract The diagnosis rests, firstly, on finding frank blood, without albumin, casts, or pus cells, in sterile urine, secondly on observation of unilateral bleeding at cystoscopy on one or more occasions, and thirdly on the exclusion of specific renal disease by detailed investigation

In a study of 7 cases of " essential renal hæmaturia " in which nephrectomy was undertaken, Somerset and Harkness[1] found that the renal cortex and medulla appeared normal but there was obvious dilatation of the small vessels of the pelvic submucosa accompanied by degenerative changes in the vessel walls and by adjacent areas of hæmorrhage Although the pelvic epithelium appeared unbroken, there was evidence suggesting migration of blood-cells through the intact membrane Finally some of the areas of submucosal hæmorrhage showed indications of a healing process—namely, small hyaline eosinophilic-staining areas in which the remains of red blood-cells were apparent On this account Somerset and Harkness are inclined to abjure operation in future cases, and they suggest that the changes seen on microscopy result from some ill-defined inflammatory stimulus or possibly a localised collagen disorder which might respond to steroid therapy But they stress the difficulty of excluding other and more serious causes of hæmaturia, and in cases of severe recurrent unilateral bleeding the responsibility of persevering with conservative management is likely to weigh heavily

FERTILITY CONTROL BY IMMUNITY

IT was once common to forestall youthful inquiries on the nature of things leading to the birth of a child by describing the reproductive functions in the birds and the bees In the present sophisticated age this practice seems to be dying out (more's the pity, for natural functions are generally clearer displayed in simpler lives), but it was fully supported by Dr Albert Tyler, of the California Institute of Technology, in an Oliver Bird lecture on Immunological Approaches to Fertility Control which he gave in London on Sept 26

Dr Tyler's interests were initially centred on the process of fertilisation in sea urchins and other marine invertebrates, and he first achieved international repute through his many contributions to this branch of zoology, wherein he has become a worthy successor to the great F R Lillie What especially commanded his attention, Dr Tyler explained, was the relationship between fertilisin, a substance associated with the surface of the sea-urchin egg, and antifertilisin, carried by the spermatozoa The normal function of these substances is connected with the entry of the spermatozoon into the egg, the prelude to fertilisation But fertilisin can easily be extracted and purified, and when a suspension of spermatozoa is treated with a solution of this substance they become firmly attached to each other (agglutinated) through the reaction between fertilisin and their antifertilisin Afterwards, the spermatozoa may separa again, but now, though still vigorously motile, they ar quite incapable of fertilisation they have been effectivel sterilised without obvious detriment in other ways Antifertilisin, too, can be extracted from spermatozoa eggs treated with it are rendered infertile because th fertilisin on their surfaces reacts with the antifertilisin t form a sperm-impermeable barrier The results certainl suggest a means for fertility control among sea urchins Fertilisin and antifertilisin have proved highly species specific, and in this, as well as in certain other features their relation strongly resembles that of antigen an antibody

The immediate prospects of controlling human fertilit by immunological methods are, as Dr Tyler freel admits, not particularly bright Studies with laborator animals have yielded conflicting reports, and serious difficulties attend the application of many of the procedures to human subjects If, for example, it becomes possible to immunise a woman against her husband's spermatozoa, it is important that she is not at the same time rendered allergic to her spouse The degree of reaction specificity required to avoid this risk is not easily attained

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[1] Somerset, J B, Harkness, G G *Aust N.Z J Surg* 1960, 29, 277

Hope for the future lies chiefly in the fact that immunology is now in a state of flux, new ideas continually being advanced and old ones overhauled, so what now seems impossible may soon become possible Among the new developments are several that may prove directly applicable in fertility control. Methods for the fragmentation of antigen, for example, are giving encouraging results, antigen size is critically important when a secluded part of the body, such as the site of fertilisation, has to be reached. The enhancing effects of the adjuvants developed by the late Jules Freund and his team are an immense help in provoking antibody production, especially by spermatozoa. Recent work has shown that antibody can be functionally modified by photo-oxidation untreated serum-antibodies against sea-urchin spermatozoa cause agglutination, photo-oxidised ones do not agglutinate spermatozoa but render them incapable of fertilisation. When serum containing antibodies against the jelly coat of sea-urchin eggs is applied to fertilised eggs, cleavage is completely inhibited, while normal serum has no noticeable effect.

These and other developments described by Dr Tyler, coupled with the fact that the use of immunological procedures in medical practice is now almost universally accepted, undoubtedly tempted his listeners to share his optimism on the ultimate prospects of fertility control through immunity

STRONTIUM 90 IN THE DIET

SINCE 1958, the radiobiological laboratory of the Agricultural Research Council has been studying the amount of strontium 90 (^{90}Sr) appearing in the human diet in the United Kingdom as the result of test explosions of nuclear weapons A countrywide survey has assessed the mean ratio of ^{90}Sr to calcium in the average diet of the population, and local studies have been undertaken in areas where the quantity of ^{90}Sr in the diet was likely to exceed the average Some further details of these inquiries have just appeared.[1]

Bulk samples of milk were prepared for analysis from milk collected twice monthly from some 200 depots handling over 40% of the country's total production. In the early part of 1959 the amount of ^{90}Sr in milk rose appreciably but later fell away so that the values in the latter part of 1959 were much the same as those observed a year earlier. The countrywide values at the end of June and December, 1959, were 11 7 and 12 2 micromicrocuries (μμC) per litre (9 6 and 9 8 μμC per g of calcium) respectively. The mean ratio of ^{90}Sr to calcium in the average diet of the whole population in 1959 is put at 9 μμC per g , and it is thought not to have exceeded 15 μμC in the diet of any large section of the population. These values are about 50% higher than the estimates for 1958, but they are less than a twentieth of the maximum permissible level recommended by the Medical Research Council.

In the local investigations, 13 farms in wet upland areas were examined. All these areas were small and only a fraction of the food consumed in them was locally produced. Assuming that an individual could consume the most highly contaminated foods of different types found in these surveys (and to do so he would have to collect his diet from all parts of the country), the ratio of ^{90}Sr to calcium in the total diet would be 80 μμC per g , but this is much in excess of the likely level in the diet of any person and is a tenth of the recommended permissible level for individuals

Despite the variables that make predictions uncertain, it now seems reasonable to suppose that the strontium released into the atmosphere has already exerted its major effect, and the levels of ^{90}Sr in the diet should decline further—provided there is no more contamination.

MOTOR END-PLATE IN MYASTHENIA GRAVIS

IN a biopsy study of the neuromuscular junctions in myasthenia gravis, Bickerstaff and Woolf[1] divide their seven cases into two groups according to whether or not histological changes were present in the muscle Their investigations were confined to muscles which showed slight clinical involvement.

Multiplication and elongation of the end-plates was noted in two of the three cases in which the muscle was histologically normal. Multiplication, according to these workers, may also be met with in conditions associated with muscle-fibre hypertrophy, and they instance spastic limbs, myotonia congenita, and dystrophia myotonica. Elongation, however, is possibly peculiar to myasthenia gravis, for it was found also by Coërs and Desmedt[2] in their report of six cases It was present to a remarkable degree in the case of congenital myasthenia gravis reported by Coërs and Woolf[3] but was absent in the third case of the present series—a boy aged 8 years with a history of only six months' duration. Multiplication of the end-plates increases the length of the synaptic area elongation would appear to increase it still more

In the second group, in which were present one or more of the degenerative changes commonly found in muscles in cases of myasthenia gravis, elongation of the end-plate tended to be obscured by excessive collateral sprouting of the terminal axons, which was especially noticeable in relation to lymphorrhages Such proliferation of nerve-fibres has been reported in several diseases in which degenerative changes are commonly found in muscle. Bickerstaff and Woolf refer to it as "myopathic sprouting" and believe it to be of functional significance in that foci of cholinesterase activity characteristic of this disease tended to be associated with the earliest sproutings—suggesting a response on the part of the muscle-fibre to contact with the growing tips of an axonal sprout.

Elongation of end-plates with abnormal branching of nerve-endings and complex terminal arrangements were noted by McDermot[4] in each of her eight cases of myasthenia gravis. She draws attention to the frequency in this disease of ultraterminal twigs sprouting from the end-plates—a finding which incidentally is also illustrated by Bickerstaff and Woolf—and in her case 5 she demonstrates the formation of a further series of elongated end-plates on one such ultraterminal twig She speaks also of swellings and irregularities involving both myelin sheaths and axons and of the occasional presence of non-myelinated fibres sometimes accompanying the others but at other times running alone In her view the anatomical evidence points to a primary neural defect which is apparently associated with abnormal resistance to depolarising agents It precedes any histological change and involves muscles other than those clinically involved, for in each case she selected for study the deltoid muscle, which was in most cases normal clinically, electromyographically, and histologically Clinical weakness is associated with low-voltage short-duration potentials, and in McDermot's view this represents the stage when the defect in neuromuscular transmission becomes partially or completely irreversible

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[1] Strontium 90 in Human Diet in the United Kingdom 1959 Agricultural Research Council Radiobiological Laboratory report, no. 3. H.M. Stationery Office. Pp. 58 3s. 6d.

[1] Bickerstaff, E. R., Woolf, A. L. *Brain*, 1960, 83, 10

[2] Coërs, C., Desmedt, J E. *Acta neurol. belg.* 1959 59, 539

[3] Coërs, C., Woolf A. L., Comptes rendus du Congrès des Médecins Aliénistes et Neurologistes. Liège, 1954.

[4] McDermot, V *Brain*, 1960, 83, 24.

The technique of intravital staining of nerve-endings introduced by Coers[5] in 1952 constituted an important advance in myopathology, and its application has already provided impressive data As Bickerstaff and Woolf have suggested, the electron microscope may shed light on the possible role of ultramicroscopic axonal sprouts which they believe may be present in myasthenia gravis

THE HISTORICAL CONGRESS

George Santayana said that "he who is disposed to ignore history must be prepared to repeat it" The Society of Apothecaries, though it has sometimes helped to make medical history, by no means wishes to ignore it, and has created a faculty of the history of medicine and pharmacy Inaugurated last year with a lecture by Canon Charles Raven which has been published in its official organ,[6] the faculty will administer the founder's lecture of the Society of Apothecaries, the Gideon de Laune lecture, in which this year Sir John Charles spoke of Roger Bacon on the Errors of Physicians[7] It also sponsors an annual students' lecture, given this summer by Dr K D Keele on the 303rd anniversary of William Harvey's death, with the financial aid of the Wellcome Trust, it maintains a full-time research fellow who is a professional historian, Mr R C Roberts, it has a panel of speakers on historical topics available to its corporate members (now including all the important medical corporations, schools, and historical societies in this country), and it will award the Maccabæans' medal and prize next spring for an original essay on a set subject by an author under the age of 30

At the first British Congress on the History of Medicine and Pharmacy, held last week under the presidency of Dr W S C Copeman, the theme of the Evolution of Medical Practice in Britain was analysed by a dozen learned and entertaining speakers, as was said of Gibbon, both "luminously and voluminously" Dr F N L Poynter, hon secretary of the faculty, said that the Apothecaries not only led medical reform in the last century but in particular introduced a set curriculum and pioneered written examinations, the latter some twenty years before the Civil Service adopted them in 1852 Dr Charles Newman, in a provocative talk on medical education, suggested that our professional conscience was born with the Royal College of Physicians in 1518 Perhaps this was the reason for Sir Charles Dodds' apologia for the college as "a bad-tempered governess with recalcitrant children" Sir Zachary Cope gave a charming account of the Royal College of Surgeons, especially as it has risen from the ruins of war The chill cast by Mr Peter Laslett, of Cambridge, over the amateur social historians, was gently cleared by Mr Michael Perrin, chairman of the Wellcome Foundation, which sponsored the congress Dr W H McMenemey, talking of medical societies, thought that even the modern doctor may be isolated, seeing his colleagues only at the local garage Dr Ffrangcon Roberts discoursed resignedly on the influence of patients, and Dr Keele elucidated the philosophy of clinical research Mr H J Malkin recalled how the obstetricians had been successively disowned by physicians and surgeons before coming comfortably to rest in their own college Dr R M S McConaghey, after interpolating that family doctors, too, like to feel that they retain an interest in obstetrics, went on to speak of rural practice, and said that in the past five years he has met no fewer than three witches Nor are such people at all behind the times, two of them are specialists who will give incantations only over the telephone Finally, Prof Douglas Guthrie insisted that the active centre of British medical practice has always been north of the Border, claiming indeed that medical knowledge is still one of Scotland's principal exports

The congress closed with a dinner in Apothecaries' Hall at which Lord Cohen of Birkenhead spoke on the Uses of Medical History He decried the notion that mere rummaging among old documents may lead to an M D thesis, and commended history to any sceptical student as giving "colour and meaning to his reading and his speech" To the embryologist all history is contemporary history, it should illuminate the present and give a vision of the future This modern psalmist sent his hearers home newly inspired to read as widely as himself As Santayana again may remind us, "there is no cure for birth or death, save to enjoy the interval"

PACKAGE ACCEPTED

No-one really expected the Representative Body of the British Medical Association, at its special meeting last week, to tamper with the "package deal" the Government had offered—a package put together by the Royal Commission and skilfully and rapidly tied up by the two joint working parties[1] And they certainly did not any proposal that threatened to loosen the string, let alone touch the paper, never had a chance, and all the representatives, bar one adventurous spirit, agreed to accept the reports of the working parties and the Government offer to implement the recommendations of the Royal Commission "as a whole and as they stand" It is true that an agenda of 146 items contained many misgivings, but none of the amendments carried real conviction—the sort of conviction that would have been needed to persuade the meeting to up-end all and start again In their hearts, it seemed, representatives acknowledged that the Royal Commission had awarded the profession a substantial triumph, though not all of them could command the frankness to ask, as Dr Solomon Wand did, "Why be ungracious now? Let us be satisfied with our victory"

The thing that bothered representatives most was the new recommendation from the joint working party on general practice that £1 million a year "should be reserved from the distribution of available money so that further consideration can be given to methods of making the best possible general medical service available to the public" This proposal generated 44 amendments for the agenda, and nearly all of them ranged between downright hostility and grudging acceptance, but one, which wins credit for the doctors of Nuneaton and Tamworth, unbent so far as to say something constructive —"that the £1 million be used to pay for additional items of service, such as casualties, minor operations, and psychiatric advice" Some more thoughts on these lines might have been helpful to the further working party which, it is proposed, should study this matter and suggest what to do As it turned out, these £1 million fears were partly subdued by Dr Wand, who had armed himself with a very recent letter from the Ministry of Health setting out the Minister's views on certain points that might be worrying representatives The letter made it clear that there was no question of the £1 million accumulating from year to year until such time as detailed agreement on a scheme for its use had been reached.

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[5] Coers, C *J Neurol Neurosurg Psychiat* 1952, 15, 211

[6] *Medical History* 1960 4, 85

[7] See *Lancet*, 1960, i, 968

[1] See *Lancet*, Aug. 27, 1960, p 482.

"The reserved sum is money which (if the offer is accepted) becomes due to general practitioners as part of their total remuneration. If, when the final calculation of monies due for the financial year 1960–61 is made, the further joint working party had not submitted agreed recommendations, acceptable to both the Government and the profession, for the use of the reserved sum this amount would be distributed as part of the final settlement for the year This procedure would continue to apply while the working party continued its deliberations"

This salve seemed at first to have soothed the irritation, but by the afternoon it had worn off sufficiently for one speaker to call the plan "blackmail" and for the meeting to declare (by 161 votes to 137) that, while accepting the working party's recommendations "as a matter of expediency", they deplored the introduction of the new matter of the reserved £1 million. Thus, though the package was prodded suspiciously, it remained intact.

IDIOPATHIC HYPERKINETIC STATE

A PERSISTENTLY raised cardiac output may result from any of several causes—notably thyrotoxicosis, anæmia, patent ductus arteriosus, arteriovenous communications, anoxic cor pulmonale, or hepatic failure. In severe cases this leads to enlargement and overactivity of the heart with systolic hypertension and a rapid, jerky pulse, the extremities are often warm and there may be finger pulsation. Usually there is a short ejection type of systolic murmur due to rapid blood-flow, and in longstanding cases heart-failure may develop, with œdema and raised venous pressure. A careful search generally reveals the underlying cause, but Brachfeld and Gorlin[1] have described 8 cases in which a persistently raised cardiac output had no apparent cause They suggest that these patients all had a previously undescribed syndrome, which they call "idiopathic hyperkinetic state"

The 8 patients were males, aged 17–48, and all except 1 were referred because a murmur had been found on routine examination. 6 patients were entirely symptom-free, and 4 of these were in excellent physical training Brachfeld and Gorlin are unwilling to attach any significance to the sex and age distribution of their series, which they regard as somewhat selected, and since preparing their paper they have encountered the condition in a young woman. The peripheral signs of high cardiac output were scanty, without sweating or rise in skin temperature, but the blood-pressure tended to be labile and systolic hypertension was often present. More than half the patients had prominent carotid pulsation with an overactive left ventricular impulse, and all had a short ejection type of systolic murmur 1 patient had mild mitral stenosis in addition The electrocardiogram was always abnormal, indicating hypertrophy of one or other ventricle, and in 4 cases it also showed changes suggesting high blood-flow and diastolic ventricular overloading Radiographs showed undue prominence of the lung vessels in half the patients, and in all fluoroscopy revealed overactivity of the heart. Extensive investigation showed no abnormality apart from considerably increased cardiac output at rest associated with diminished peripheral resistance There was no clinical or laboratory evidence of any of the accepted causes of a high output state, and in particular intracardiac or extracardiac shunts were excluded, the conspicuous lack of symptoms and the normal serum lactate and pyruvate levels during exercise were considered good evidence against both vasoregulatory and neurocirculatory asthenia Anxiety was naturally suggested as a possible cause, but repetition of cardiac catheterisation after heavy sedation or during sleep showed no significant fall in output

Brachfeld and Gorlin point out that, in the absence of any striking signs, this syndrome can easily be overlooked in patients who present merely with a systolic murmur, and they suggest that some patients with so-called functional murmurs may really have the idiopathic hyperkinetic state They believe that the syndrome is due to a defect of central regulation of cardiac output, although they have no direct evidence of this Whether the persistently raised output ultimately leads to heart-failure is clearly important. So far this has not been established; but 1 patient in this series had cardiac enlargement and left ventricular failure at the age of 27 without any other cardiac abnormality The idiopathic hyperkinetic state may be found to underlie previously unexplained cases of heart-failure.

BARIUM-SULPHATE EMBOLISM

IN a striking case reported by Truemner et al[1] a 76-year-old woman died suddenly during a routine barium-enema examination. The death was thought to be due to heart-failure, and this was supported by the gross post-mortem findings By chance a very detailed necropsy was done, and it was demonstrated beyond doubt that pulmonary capillaries had undergone massive embolism by barium-sulphate crystals, even though there was no evidence of injury to the lower intestinal tract. Search revealed a report of only one other proven case of this accident, and it can probably be assumed that death from this cause is extremely rare But Truemner et al point out that barium-enema examination is often followed by transient fainting attacks and other reactions usually dismissed as emotional or reflex, and these, they argue, may well be due to embolism

It is salutary to be reminded that such an accident can happen many routine radiographic procedures carry a definite, though slight, risk which may be forgotten in the haven of the X-ray department. It seems that in this fatal case the contrast medium was introduced blindly into the rectum, with a bag inflated to prevent reflux. There was, as it happened, a simple stricture in the sigmoid region of the colon, and between these two points enough pressure was built up to allow barium somehow to find its way into the submucosal venous bed of the rectum and anal canal A radiologist, watching the march of events under the screen, is made aware of such an increase in pressure by ballooning of the rectum and is thus warned of impending danger. In the ordinary way this should be an adequate safeguard.

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[1] Brachfeld, N., Gorlin, R. *Brit. Heart J* 1960, 22, 353

[1] Truemner, K. M., White, S., Vanlandingham, H. *J Amer med Ass* 1960, 173, 1059

BRONCHIOLITIS IN INFANCY

THE acute respiratory diseases of childhood are difficult to classify. They are in general mild and non-specific, and are labelled with more facility than thought by such terms as bronchitis, pneumonia, bronchopneumonia, and bronchospasm. From this terminological hotchpotch some well-defined entities are emerging. It is now clear that asthma often has its origins in infancy, and the history of " teething bronchitis " and " pneumonia " so often obtained from the child asthmatic represents not infective illness but the true wheezing and dyspnœa of infantile asthma. In infants cardiac failure presenting with respiratory distress is often wrongly diagnosed initially as " pneumonia ".[1]

Most investigators of respiratory illness in infants are confident that " bronchiolitis " is a more or less distinct entity. It is an important disease because it is serious and alarming and has a high mortality. The incidence is difficult to determine because of diagnostic confusion, and in cases where the infant dies at home the death is probably often certified as due to bronchitis or bronchopneumonia or even convulsions. The severe form of bronchiolitis arises in infants under the age of 18 months. The affected infant has an initial or prodromal illness which is mild and coryzeal. Commonly, other members of the family have had recent or have contemporaneous " colds ". The infant's " cold " may be febrile, and mild gastro-intestinal symptoms may accompany the snuffly rhinitis. The prodromal illness persists for a few days—sometimes a week or more—after which the infant's condition deteriorates with dramatic rapidity. The slightly noisy breathing and laryngeal cough of upper respiratory catarrh is replaced by urgent dyspnœa with rapid, grunting respirations and rib recession. The temperature and pulse-rate rise rapidly, perhaps with a convulsion. The obstruction to ventilation causes hypoxia, so the child becomes restless, exhausted, and cyanosed. In the most severe cases cardiovascular collapse occurs early, and in a few hours the child appears moribund. In less severe cases, exhaustion and dehydration precede terminal collapse. The severity of the illness is better judged from the general appearance of the child than from auscultation of the chest. There may be no abnormalities in the breath sounds, and adventitious sounds may be absent or comprise fine rales throughout the lungs.

The ætiology of the condition is uncertain. The epidemic nature of the illness, its association with familial respiratory infection, and the preceding upper-respiratory illness, all suggest an infective cause, but no pathogenic organism has been consistently implicated,[2] and antibiotics have not been clearly proved to be effective.[3,4] The failure to identify any one pathogen may be due to the fact that the disease represents a non-specific inflammatory response to various organisms, or it may simply reflect the difficulty of obtaining specimens of secretions from the lower respiratory tract of small children. The histological appearance of the bronchial tree in fatal cases does not clarify this issue. The dominant finding is blockage of the finer bronchi and bronchioles by mucus plugs or mucopurulent secretion, and inflammatory swelling of the bronchiolar epithelium. There is congestion and exudate which is mononuclear rather than purulent.

The treatment of bronchiolitis has been directed toward the maintenance of oxygenation, the elimination of bacterial infection, and the correction of other life-threatening complications, such as dehydration, cardiac failure, or hyperpyrexia. Dugdale and McGeorge[5] have suggested that in severe cases large and repeated doses of adrenal corticosteroid hormones may be beneficial: 100 mg. hydrocortisone hemisuccinate by intramuscular injection every four hours is suggested. This report gives added weight to the impressions of others concerning the usefulness of these drugs. It seems reasonable to add this or another anti-inflammatory steroid to the administration of antibiotics and oxygen.

Reporting an epidemic of bronchiolitis in 1953, Heycock and Noble[6] suggested that, on follow-up, the survivors seemed more prone to wheezy bronchitis than children in the general population. Further follow-up studies might perhaps not only shed light on the ætiology but also indicate the degree of residual damage, if any, following severe bronchiolitis.

THE CHIEF MEDICAL OFFICER

Sir John Charles, chief medical officer of the Ministry of Health, the Ministry of Education, and the Home Office, is retiring from the public service on Nov. 30. He has been chief medical officer since May, 1950.

The Minister of Health, the Minister of Education, and the Secretary of State for the Home Department have appointed Dr. George Godber, a deputy chief medical officer in the Ministry of Health, to the joint post from Dec. 1.

Dr. Godber was born in 1908, and was educated at Bedford School, New College Oxford (where he represented the university at rowing), and the London Hospital. After service with the London and Surrey county councils, he joined the staff of the Ministry of Health as a medical officer in 1939. He was appointed senior medical officer in 1946, principal medical officer in 1948, and deputy chief medical officer in 1950. During the late war he was a principal regional medical officer in the North Midlands region, and he undertook with the late Sir Leonard Parsons and Mr. Clayton Fryers a survey of the hospital services of the region. As deputy chief medical officer he has been particularly concerned in the administration of the National Health Service. He has visited the United States, Scandinavia, and Brazil to study the health services in those countries, and has been a member of a number of seminars of the World Health Organisation.

INDEX TO THE LANCET

FORMERLY the index was sent only to those who asked for it, but now it goes to all subscribers. The index and title-page to vol. I, 1960, which was completed with the issue of June 25, is enclosed with each copy of our present issue.

As we may not be able to supply indexes to binders, orders for binding the collected issues are best deferred until the index can be sent with them.

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Special Articles

MOTOR-CYCLE ACCIDENTS

Protection from Crash Injuries

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LAST year, motor-cycle and motor-scooter accidents accounted for 1592 deaths, 25,613 serious injuries, and 64,034 slight injuries (Ministry of Transport 1960) Compared with the previous year, this represents an increase in casualties of about 23%, though "vehicle-miles" travelled have increased by only 17% The figure is the more distressing as most of those killed and injured are young

A good deal of attention has been given to crash helmets and protective clothing, which are of some value because in many motor-cycle accidents the rider is thrown from his machine, and severe head injuries can result if he lands on his head. Little effort, however, appears to have been made to find out whether retention in or on the motor-cycle might be safer than ejection on the crash helmet

Distribution of Injuries to Motor-cyclists

Less study has been made of crash-protection for motor-cyclists than for car drivers Most of the work has been done in the United States, where there are fewer motor-cycles than in this country, and this may account for the discrepancy Preventive work on motor-cycle accidents stems largely from the researches of Cairns on the significance of the crash helmet in prevention of head injury Cairns (1941) reported that of over 100 accidents 92% resulted in head injuries and 66% in multiple injuries The incidence of fractures to the lower limbs in motor-cycle accidents was higher than in other types of accident. In subsequent papers Cairns and Holbourn (1943) and Cairns (1946) drew attention to the correct design of helmet, the better types of which reduced the incidence of skull fracture by three-quarters

The committee on road safety in its final report (Ministry of Transport 1947), taking into account the work of Cairns, suggested that crash helmets might be made standard wear for civilian motor-cyclists

An analysis of 579 accidents to Army motor-cyclists (Bayly Pike 1949), confirmed the high fatality-rate in head injuries, which accounted for 25% of all serious injuries

A review by Starks (1952) showed that 50% of the civilian motor-cyclists admitted to hospital had head injuries—twice the head-injury rate for Army motor-cyclists, who wore helmets 35% of civilian riders and 50% of Army riders had injuries to the lower limbs More than half the motor-cyclists injured were men under 27 years old, and three-quarters were under 35

Further reports by Lewin and Kennedy (1956), Chandler and Thompson (1957), and Starks and Lister (1957) have confirmed the value of crash helmets and the importance of head injuries as a cause of motor-cycle fatalities

Bauer (1957) gives the distribution of serious injuries to motor-cyclists as head, 49 6%, legs, 26 8%, arms, 12 5%, lateral aspects of the thorax, 5 9%, shoulders, 1 8%, pelvis, 1 7%, and buttocks, 1 5%

Grime (1958) referred to the 80% head injury death-rate in motor-cyclists and said that, for equivalent mileage driven, a motor-cyclist is about 40 times as likely to be killed as is the driver of a four-wheeled vehicle. He felt that this difference might be accounted for by the rider being flung from his machine and by the absence of protective devices from the motor-cycle.

An analysis for 1956 of the number of motor-cyclists killed per 1000 injured showed that with crash helmets, on roads with speed limits, the rate was 12 9 compared with 14 8 without helmets On roads without speed limits the corresponding figures were 35 5 and 39 9 (*British Medical Journal* 1957) Since then much work has gone into the design of helmets, but according to Gissane (1959) less than 50% of motor-cyclists wear them

Car Crash Research

The mechanics of car crashes and motor-cycle crashes are similar In both cases a moving vehicle is rapidly decelerated and the momentum of the driver, passenger, or rider causes him to continue in the original direction unless there are appropriate restraints

In car accidents protection is based on proper packing of the human frame inside the "container" (the car) No other readily damaged and valuable article would ever be sent packed loose in a container which is going to be subjected to buffetings, sudden stops, crashes, and other violent treatment Ways of retaining and restraining the movement of the driver and other car occupants and their correct "packing" in the vehicle have therefore been the basis of much research on which the following observations are based

1 The more closely the occupant is constrained in the accident, the safer he is, movement forwards and ejection via doors and windscreen have been shown to be highly dangerous (Moore 1958) Hence the development of lap and shoulder straps, as in some aircraft (Odelgard and Weman 1957)

2 To prevent injury on sudden stoppage, both the removal of lethal projections and the provision of special crash-padding are useful. The telescopic wheel, the chest-padded wheel, the removal of projecting handles, and the use of force-absorbing facia boards (McFarland 1955) are all means to this end.

3 The effect of overall design on the strength of the "box" (car) and hence the ease with which the "package" may be crushed is an important factor The relative merits of various types of car construction in resisting impact deformation have been discussed by Starks (1958)

These means of protection against injury in car accidents are not yet sufficiently well known to the public They are not required by law and therefore manufacturers do not have to provide them For example only one manufacturer in this country has incorporated provision for safety-harness in a vehicle, though safety belts are not fitted even to that car as standard equipment Extra cost is usually cited as a barrier to their application

In spite of all that is known, anti-crash measures are not put into operation and in-crash protection in the car hardly exists Yet it is likely that correctly designed and fitted safety-harness alone has a prophylactic value in accidents comparable to that of immunising agents against infectious diseases, and, when combined with other protective features, its value might be even greater Such a time-lag between acquiring the basic knowledge of an answer to a problem and its application appears to be so common as to be the rule in public health.

Protection of the Motor-cyclist

Retention and adequate padding pay dividends for the car driver and occupants, but for the motor-cyclist protection is almost entirely lacking

It is odd that while the desirability of retention has been so widely accepted from car-crash data, we continue to believe that the motor-cyclist should be thrown from his machine with no more that a crash helmet to absorb the force of the impact (fig 1)

It has been stated, though there is little supporting

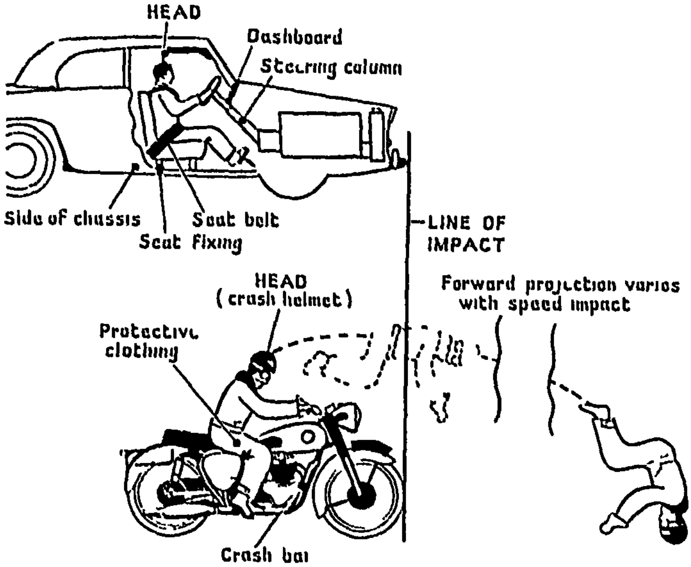

Fig 1—Contrasting situations in crash protection

In the car retention and protection are the objects In the motor-cycle there is no protection, and ejection is frequent with only crash-helmet protection for the head on landing

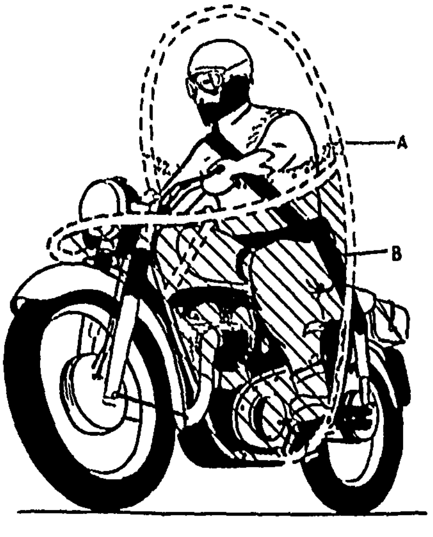

Fig 2—Suggested experimental design of roll and crash bars l machine fitted with seat-retaining straps

The suggested safety belt is attached at its lower extremity to th top of the rear suspension " leg " with a further suggested strap in the region of shoulder level " A " to protect against " jack knifing " of the body under deceleration A diagonal shoulder strap is als shown to prevent extension of the lumbar spine which might occur i only a waist or thigh-level strap was used Shaded area between rol bars enclosed for leg protection

experimental or field evidence, that motor-cyclists trapped on their machines suffer more than those ejected, but this probably refers to accidents where the impact is so severe as to be lethal in itself The effectiveness of retention would undoubtedly depend on the protection provided at the same time

The only references which have been found to the possibility of the use of safety belts for motor-cyclists are brief ones by Grime (1954, 1958) In referring to the extra leg protection offered to riders by scooter-type machines, he suggested that a motor-scooter design might be attempted in which the rider was completely enclosed in a saloon body He though that " investigations might profitably be made to find the best method of strengthening the body work to afford protection in accidents, and also to determine whether on such a machine the rider would be less likely to suffer injury if he were tied to his machine by safety belt " Grime showed a photograph of such an enclosed scooter Instability in side winds is however a disadvantage of completely enclosed two-wheeled vehicles

Before automotive crash research had been undertaken, it was a common belief that it was a good thing to be " thrown clear " in a car crash Statistics make it clear that this is not true (Moore et al 1957), but this view is still widely held, and it is common to hear of people " escaping injury by being thrown clear of the accident "

The most important cause of fatalities in motor-cycle accidents is head injury, followed by injury to legs and arms Retention on the vehicle by safety belt would prevent most head injuries but it would still be necessary to provide suitable body protection to avoid injury by direct impact, it would obviously be unsatisfactory to prevent the head injury of ejection if bodily injuries were aggravated by side-swipes, dragging, and involvement with the machine Occasionally the head may be struck while the rider is on the machine, retention is then irrelevant, but protection of the head is still essential

Motor-cyclists are " on " their machines rather than " in " them, and provision of protection for existing designs is thus more difficult and additional devices must be built around the vehicle Such safety devices could constitute part of the original frame of the machine rather than something added afterwards A design for safety need not be retrograde in terms of speed, controllability, or streamlining, indeed it may well have incidental advantages for any of them We cannot legislate out the masculine propensity for speed, we can, however, give built-in safety Crash protection would help to prevent injury in spite of human error and irrespective of conduct, training, and experience, the size and stability of the machine (Ministry of Transport 1952) or the role of anti-skidding braking systems (Commissioner of Police 1959, Ministry of Transport 1959)

Protection by Safety-belts and Roll-bars

It is possible that the best protection to the motor-cyclist would be afforded by a combination of some form of retentive harness and suitably shaped roll-bars as shown in fig 2

The anchorage could be at the top end of the telescopic " legs " of the rear wheel suspension, and the straps should fasten to a belt, possibly over the hips, joined front to back

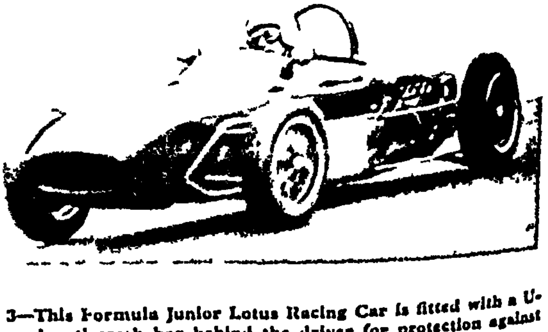

Fig 3—This Formula Junior Lotus Racing Car is fitted with a U-shaped anti-crash bar behind the driver for protection against injury in case of a roll-over (*Autosport*)

by a diagonal strap passing over one shoulder, in order to avoid undue extention forces on the sacro-iliac and lower lumbar veterbral joints Some "jack-knifing" could occur with a belt anchored low down in this way and the "lap" straps with low anchorage should be combined with a shoulder harness attached to parts of the vertical crash-bar as in the diagram

Protection against being catapulted forwards necessitates retention on the machine, but there must be protection against injury in the evolution of the accident Roll-over injury is guarded against in motor-racing by roll-bars (see fig 3) which are becoming commoner, and one official formula for racing car design specifies their provision The Indianapolis speedway cars must incorporate both a roll-bar and seat straps

Roll-bar protection would have the advantages of not changing greatly the appearance of the machine, of providing protection in the simplest way, and of being easily fitted to existing motor-cycles and motor-scooters These bars would not affect stability in cross-winds

Experiments with various types of roll-bars appear to be the only way to determine the best shape Roll-bars would require careful design to allow easy clearance for the machine in traffic, and to avoid their becoming in themselves a cause of head injury It is not suggested that the rider should be shut in a cage, but rather that the existing type of crash-bars, providing leg protection only, should be extended to play the same part as the roll-bars fitted to racing cars

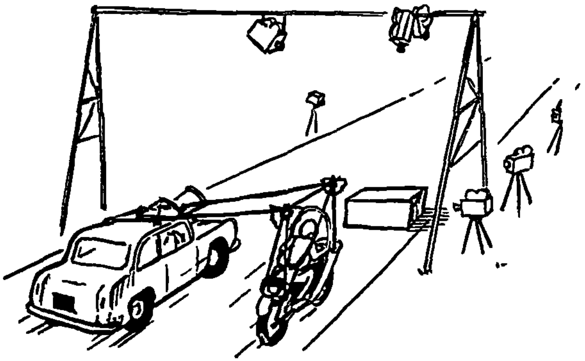

Fig 4—Machine with safety fittings towed alongside car at the end of quick-release arms so that the machine can crash into barrier Subsequent evolution of fixed and free dummy riders can be photographed by high-speed cameras on the superstructure above the barrier

Suggested Experimental Arrangements

In a restricted way it may be possible to make comparisons between the extent of injuries to riders known to have been ejected and to riders known to have remained on the machine after having been struck A field study to determine this could be made, but it is clear that the final answers depend on observing, under controlled conditions, the evolutions of crashing motor-cycles fitted with anthropometric dummies, strapped on and loose, and on the effect of various forms of crash protection such as roll-bars

Various arrangements are possible to simulate crash conditions (1) the motor-cycle might be towed on outrigger from a car with a quick-release device (fig 4), (2) projected and driven along a guide-rail by outrigger wheels (fig 5), or (3) it could be rotated in a large circle at the end of a radial arm This third method might give most control over the conditions of crashing and facilitate observation, but it would be much the most difficult to set up and the evaluation of results might present some problems

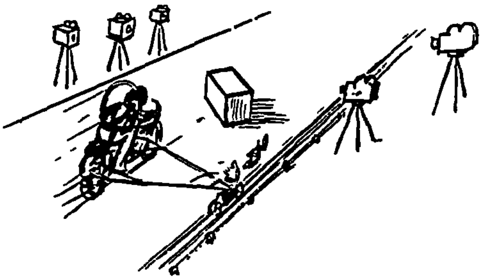

Fig 5—The machine is guided to the barrier by a rail and outrigger wheels both of which are released just before impact

A fertile field clearly exists for experimental work to determine whether safety belts are applicable to the motor-cycle, whether in some circumstances, they require quick-release devices, and how they could best be combined with safety roll-bars or hoops

This information could be readily obtained by experimental work using techniques similar to those used by Gerlough (1954), Severy and Mathewson (1956), and Severy, Mathewson, and Siegel (1959) on car work in California The evolution of dummies, both with and without retention and protection, could then be assessed for the first time and the impacts and injuries to which they are subjected in the experimental situations determined

Summary

Motor-cyclists are particularly vulnerable to head injuries, against which their only protection is a crash-helmet Work in the United States and in Sweden has shown that retention within the vehicle affords the greatest protection to car drivers and the same principle could be applied to the protection of motor-cyclists

A way of applying retention by safety straps together with protection by anti-crash bars encircling the machine in the vertical and horizontal planes is described and the need for experimental studies of crashing motor-cycles is indicated

Three possible experimental arrangements for controlled observation of motor-cycle crashes in which anthropometric dummies could be used are suggested

I am grateful to Prof R. C Wofinden for permission to publish this paper My thanks are due to members of the staff of the Road Research Laboratory for kindly reading the paper and offering helpful criticism I am indebted to The Ashley Studios for producing the various diagrams from my sketches The photograph of the Lotus racing car is reproduced by courtesy of *Autosport*

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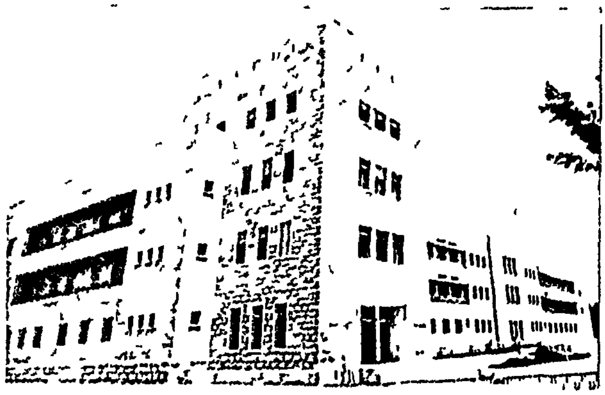
NEW OPHTHALMIC HOSPITAL OF THE ORDER OF ST. JOHN IN JERUSALEM

On Oct 11 the new Ophthalmic Hospital of the Order of St John is to be opened in Jerusalem by Lord Wakehurst, Prior of the Order. It will be the most important and up-to-date ophthalmic hospital in the Middle East and includes research units for work on the causes and prevention of diseases of the eye, a post-graduate school for doctors, and a training school for Arab nurses (male and female)

In 1946 the late Lord Webb-Johnson was appointed Hospitaller of the Order, and he set about equipping, repairing, and expanding the Order's existing hospital in Jerusalem which had suffered during the war, and by 1947 it was the most modern eye hospital in the Middle East Soon after the modifications were completed the Arab-Israeli war broke out and the hospital had to be evacuated These difficulties, however, made the Order more determined than ever to go ahead with its fight against eye diseases, and Sir Stewart Duke-Elder, the present Hospitaller, accompanied by the secretary of the Order, travelled widely in the Middle East to survey the problem of eye diseases and to explore the possibilities of coordinating ophthalmic work throughout the Middle East As a result of this survey and enthusiastic support from heads of State and industrialists the Order decided to develop a research programme and to improve treatment and preventive measures


The new St John Ophthalmic Hospital in Jerusalem

A site was quickly bought and the first buildings to be completed, at Sheikh Jarrah early in 1956, were the research laboratories, where a team, under the auspices of the Medical Research Council, set to work Already the virus of trachoma has been isolated, a great step towards improved treatment and prevention of this disease

In November, 1958, Lord Bossom went to Jordan to arrange the beginning of work on the main building, designed by Mr J E Simpson, A R I B A, and construction progressed rapidly In March, 1959, the two cornerstones were laid, one by the Chancellor of the Order, Lieut-General Sir Henry Pownall, and one by the Hospitaller

The hospital, which has cost £325,000 to build, has 70 beds and the means to treat up to 200,000 outpatients a year The warden, Dr A J Boase, has been joined by a British registrar and two British junior surgeons, a British matron, assistant matron, sister-tutor, and two sisters, and ten Arab male and ten female nurses

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Medical Education

BROADENING THE CLINICAL APPROACH

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Partly because of the organic orientation of medical training and partly because the student has only a brief period in which to become acquainted with the gamut of disease, the emphasis of clinical training still tends to fall upon the disorder rather than the patient In the belief that the balance can best be restored by causing the student to undertake some positive action in respect of the patient rather than the case, I have introduced two methods into my clinical teaching

The Relatives' Round

The person in bed in hospital, or in the outpatient clinic, can hardly be seen as the man he is, since he is robbed of his background This is partly restored by seeing the relatives, or those with whom he lives The student also needs to be trained not only in keeping relatives informed but also in talking to them To serve these three purposes I have arranged occasions when relatives could be interviewed by dressers, under my surveillance No less important, this ensures that I see relatives, and can satisfy myself that they know what is being done for the patient and also that they see me

Method

An hour is set aside before visiting time on one evening each week, no more than three interviews can be conducted during the period of one hour Those to be interviewed are selected on various grounds for example, the need for explanation of treatment or prognosis, the need to ensure, and make arrangements for, a proper reception after discharge from hospital (as for example the arrangement of care by the family during convalescence of an elderly patient living alone), or a request from the patient or the relatives themselves The rounds are not compulsory, for there is no need to make them so, since the students are anxious to attend Nor are they regular, for unless they take place only when needed an element of artificiality will prevail and so cause a failure of attendance by the student, besides making an improper demand on the relatives' time Before arranging for their attendance, it is very important to ask the patient whether he would like his relatives to be seen, for not only would any other course be improper, but if it comes to the ears of a patient that his wife, say, has been interviewed without his cognisance, he naturally fears the worst about himself

At first, interviews are conducted by me, in order that the student shall gain confidence through example, later the student conducts the interview in my presence, explaining all that is required—even a bad prognosis—and answering questions The student is asked whether he wishes to undertake the interview, so that he may refuse if he feels unprepared, he is not *told* to do so, since it is a considerable ordeal for him (or her—though women students are usually more at ease than men in this role), and the principle of "throwing him into it" destroys confidence in the sensitive and encourages superficiality in the brash Embarrassment is overcome by explaining to the relatives that the doctor (student) is helping to look after the patient (which indeed he is, or should be), that he fully understands the case, and that he will explain it to

3 Owing to his length of stay and his administrative attitude, he has become very critical of how the ward is managed

4 From his knowledge of his condition he considers that he is of little interest and in fact thinks he is a nuisance

I think that most of his behaviour is due to his slow progress something which " annoys " a man of action He is on phenobarbitone in order to keep him quiet for most of the day

This student was reviewing the case not at its outset but halfway through the period of hospital treatment His appreciation of the patient's personality was very near the mark His point 4 was shrewd, I took the hint and made my routine visits to this patient less perfunctory in character, the patient rapidly became quieter and less aggressive

Assessment 4 (the diagnosis is immaterial)

I feel that he is in some way mentally maladjusted and should not be discharged now that he has refused operation Even if discharged, it doesn't seem that he would return to work immediately He said he thought he would need 3–4 weeks' rest first

He seems introverted, perpetually pointing out his troubles and difficulties but having no drive to make him work to overcome these difficulties

I wondered if, after more investigations showed that operation was necessary, it would be possible to get Dr Fletcher to come and with Mr Brooke point out the desirability of operation as this may increase his confidence in the outcome

On the other hand he seems to need an outlet for his worry and a reason for lack of activity, all of which are provided by illness He seems to have no genuine desire to work, so could be exaggerating minimal symptoms for this purpose If so, this would explain his disinclination for an operation

This student's fine appreciation calls for no further comment than to say that we followed her advice—and laparotomy was accepted after Dr Fletcher, the physician-registrar who had looked after the patient, had restored confidence

Summary

Two methods are presented as an extension of the usual forms of clinical bedside teaching, in order to emphasise to the student the patient in contrast to the disorder

Public Health

Diphtheria in Liverpool

In Liverpool a girl, aged 8, became ill with a sore throat on Sept 18 and next day she complained of stomach pains and later vomited during the afternoon she became more and more restless On Sept 20 she was much worse, her mouth was swollen and she vomited copiously The doctor was called and she was admitted to hospital where she died from diphtheritic myocarditis on Oct 1 Her throat and nasal swabs were positive and the organism was a virulent mitis type

A classmate, aged 7 years 11 months, was found to be a carrier of virulent diphtheria organisms She was admitted to hospital on Sept 25 All this child's family, who had two weeks earlier returned to this country from a five weeks' holiday in Cyprus and consisted of mother, father, brother aged 6, and sister aged 9, were examined, and the sister also proved to be a carrier

The family of the little girl who died, consisting of mother, father, brother aged 11, and two sisters aged 13 and 6, were all found to give negative results for diphtheria on first examination, but while the second swab was being taken on Sept. 27 the little sister aged 6 complained of a sore throat and was slightly off colour She now had virulent diphtheria organisms in her nose and throat and was admitted to hospital

None of the children (clinical cases and carriers) involved in this outbreak had ever been immunised Immunisation of all contacts was undertaken immediately the diagnosis of the first case of diphtheria was confirmed

In England Now

A Running Commentary by Peripatetic Correspondents

How pleasant to think that we may once more become the cynosure if not the envy of the modern world. The Windy Hall boys are busy commissioning our new Whole Body Monitor We shall look forward to the passing-out parade We rather care for their terminology—commissioning so nicely underlines the officer status of modern automation to rule the other ranks of common flesh and blood, and Monitor has the familiar reassuring secular Big Brother touch Alexander Pope put his finger on the right button when he wrote, "Presume not God to scan, the proper study of mankind is man " Two hundred and fifty years later we are about to do just the very thing with the aid of electronics to scan us There should be plenty of scope Our Cumbrian skies have been variously described as a majestical roof fretted with golden fire, or a pestilential congregation of vapours, according to which side of the chain-link mesh the loyalty lies We have sat under the leak from reactors, under the fall-out from bombs It should be fun to see if the fission is still going on inside us, probe into the corners where it lurks, dig out odd isotopes for spectrometry, and count our rate of decay It is so difficult nowadays for us dalesfolk to regulate our lives when the Yanks keep knocking as much as 66% off permitted lifetime radiation doses Whole Body Monitor should guide us towards a new scintillating future We know what 47 chromosomes can do, and we will let the world know how we get on with 48 and 49 when we have rearranged our genes

But confidentially, we are rather proud of our Whole Body Monitor It is such a refreshing return from narrow specialisation towards the concept of the Whole Man perhaps not one of the most advanced ideas of its kind in Europe, but one more step back towards that grasp of the wholeness of things which distinguished classical Greece from the barbarians It will be interesting to see whether Monitor will beat Plato and Aristotle in finding out what makes man tick

* * *

Pure specialisation is of little value in Ireland. My early enthusiasm for orthopædics had waned gradually over the years, but our holiday in the Republic reawakened interest. Social activity each night alternated between our caravan and the local Ceilidhe house, where the inhabitants gathered around the turf fire and poteen and porter were the catalysts and the crack was good

Deep gloom, however, descended on this happy community one Saturday evening when the only young bullock was found with a broken leg The break was clean, complete, and above the hock It was in no way immobilised by a 3 in plaster bandage applied by a somewhat inebriated member of a sister profession called urgently from the local golf club Ethics, or no ethics, we felt that more plaster was needed, but a thorough search of the two neighbouring towns produced only three 4 in bandages A cross-border raid was the only solution and we returned armed to the teeth. By the light of a torch, the use of our towing rope, two sacks, and four local stalwarts, the 4 cwt black bullock was suspended from the rafters The resultant white plaster was a credit to the profession, and the celebration which followed was worthy of a more noble setting.

For three days and nights we carried our heads high and the bullock returned to the after-grass When the plaster dropped off on the fourth morning our reputation fell with it A ray of hope appeared when the lady in the next caravan said her husband might help A long and expensive telephone call, a frantic search for scrim bandage, some boiling pitch, a rope for leg traction, a finger in each of the beast's nostrils, and a man who knew what to do produced a beautiful, shiny, adherent black cast which hasn't slipped yet The bullock is back in the field, all the poteen is drunk, I'm back in the hospital, and we are planning to visit a different part of Ireland next year

* * *

In my young days money was tight, so when I came home from the hospital I changed into old clothes and dug my garden It was a task I did not really enjoy, but I was always well pleased with the result of my labours

As I grew older and prospered, I paid a man to dig my garden and plant my potatoes for me, and I wore good suits

Now, when I have more money than ever I will need, it is my delight to don old clothes and dig my own garden As I stop for breath I think—the potatoes you plant and gather yourself taste much sweeter than any other

* * *

How lacking in poetry are the names of modern drugs What vendor, crying his wares, could get any emotion into, "Who'll buy my Methyl-1 1-itsy-bitsy-pheny-bikinilamide hydrochloride!", be it ever so dextro-rotatory, and anyway if you want to prescribe a drug it's a help to be able to spell it Emil Fischer solved the problem when he named his discovery 'Veronal', after the town of Verona where his train broke down With British Railways to help, our choice could become embarrassingly large Electric computers have been used to "synthesise" new names, but it will be some time before they come up with anything to rival the "Elixir Grandior, or Aurum Potabile of the Ancients, and Sovereign Restorative for Health and Long Life", as prepared from "the Elixirated Fountain of Sanative Virtue", by Jasper the Hermit, who would not have recognised a benzene ring if you had hung it round his neck It was therefore refreshing to be asked recently by a patient for "some of them capsules of tranquillity", even if he left hastily on being told, "Thy wish is my command, O Vehicle of 1000 Unedifying Disabilities!" For a long minute I had been back in Old Damascus, When shadows pass gigantic on the sand, And softly through the silence beat the bells, or at least, between noon and 7 P M they do

* * *

The following is an extract from the minutes of a health subcommittee less than 30 miles from one of Africa's capital cities

> "The Secretary reported that she had seen the Police Officer who said that he was unable to patrol the dispensary grounds as there was no patrol going round that area during the night He said that there was always a sentry on duty who would hear if there was trouble in the dispensary A whistle had been purchased, and the Hospital Assistant had, himself, bought bow and arrows, he was warned that he must have a permit for these"

* * *

My twelve-year-old daughter to father of friend of last year's holiday "Where's Paddy this year?"

Father "Oh, Paddy has gone to Biarritz"

My prodigy "What's a ritz?"

* * *

I am no specialist in charnel houses, but I think the round stone one resembling a dovecote at Maria-Worth in Carinthia must be one of the most charming Such a narrow strip of rocky ground surrounds the Gothic parish church on the little peninsula in the lake that it must have been filled with graves at an early date, and the charnel house built for the bones excavated in digging new ones (Was it Rose Macaulay who said that Catholic cemeteries always looked so much more lived in?) You can see the bones through two grilles, in one part neatly sorted and stacked and in another skulls, pelvises, and large and small bones all jumbled together I was moved to appropriate verse, but, after rhyming "acetabulum" with "worms' pabulum" and "tourists' banter" with "great trochanter", thought I had better give it up However, the adjacent Rosenkranzkirche (10th c) provided an appropriate comment in the shape of a tablet inscribed 17 DIE SEPTEMBRIS MDCCCXCIX HOC LOCO FRANCISCVOS JOSEPHUS I GENUFLECTENS ADORAVIT DEUM

Caesar! To whom ten races bent their head
You hedged your bets and bowed your knee to God
A single score of years had scarcely sped—
Your Empire's dust and you beneath the sod

Letters to the Editor

CHRISTMAS GIFTS FUND

SIR,—Once again I ask your readers to give support to the Christmas Gifts Fund organised by the Royal Medical Benevolent Fund

Although we are able to give far larger regular grants than in the past, it is difficult for our subscribers to realise what extraordinary joy and happiness the Christmas gifts bring to our beneficiaries, to each of whom last year a gift of £8 was sent To the old, the poor, and the lonely, Christmas Day only too often brings poignant memories of happier days gone by, and the arrival of our gift gives great pleasure, as the letters of thanks testify so vividly

The magnificent response to these annual appeals shows that they touch a special chord of sympathy Because of this I appeal to you all to help bring Christmas cheer into the homes of many of our less fortunate brothers and sisters

Please send your contributions marked "Christmas Gifts" to the Royal Medical Benevolent Fund, 37, St George's Road, Wimbledon, London, S W 19

R. M HANDFIELD-JONES
Chairman Committee of Management,
Royal Medical Benevolent Fund

ALCOHOLISM

SIR,—Your annotation of Aug 20 refers to the lack of attention the problem receives from the Government of this country This would seem to apply especially to the Board of Education in that it has recently made a considerable reduction in the attention it gives to the subject in its handbook *Health Education*—a handbook of suggestions for the consideration of teachers and others concerned in the health education of children and young people

In the 1940 edition there was an excellent chapter on alcoholism which was headed with the quotation from the report of the Royal Commission

> "We accept the view that every child ought to receive specific and systematic instruction as to the properties of alcohol, as in all other matters which may affect future health, so that the child may at least be in possession of sound material on which to form a personal judgment when years of discretion are reached"

The chapter consisted of ten pages of factual information concerning the effects of both large and small quantities of alcohol upon the human body In the 1956 edition, however, all the information relating to the properties of alcohol is confined to a little over one page of a chapter on Drugs, Alcohol, and Tobacco All accurate experimental findings have been omitted and there is reference only to the ill-effects of heavy drinking no information is given about the effects of small quantities of alcohol upon such activities as driving a car Yet the closing reference to alcohol reads "Nevertheless, during the years 1954–56 convictions for drunkenness amongst persons under 21 have increased, and there are therefore no grounds for complacency"

As the soundest basis for achieving a reduction in alcoholism in this country is education of the population, and especially of the children, the Board of Education would seem to have taken a most unwise and short-sighted step in reducing in this way the information concerning alcohol available to teachers and, through them, to our children

Department of Child Health,
University of Liverpool.

JOHN D HAY

COSTS IN THE HEALTH SERVICE

SIR,—I was very interested in Dr Seale's article of Sept 24 I should like to take issue with him on his statement that, in the local health authority services, costs are largely unrelated to use

For example, to consider a local-authority midwifery service, in Bolton there are approximately 2400 births a year of which approximately 440 (18%) occur at home To deal with this number of domiciliary deliveries the authority at present employs seven midwives If half the births occurred at home (1200), then we should have to employ considerably more midwives, at least eighteen Another example is the ambulance service If the number of patients carried doubled, the authority would have to provide many more vehicles and staff

These two examples show, I think, that local-authority costs are related to use, although it must be agreed that if half the births in Bolton did occur at home, then there would be a considerable reduction in hospital staff and probably a lower overall cost to the community Dr Seale may consider it is wrong to look at his views on these costs out of context and that such changes as mentioned are unlikely, but I do think that the statement in his article is misleading

Health Department,
Bolton

A I ROSS
Medical Officer of Health

THE CIRCULATING CANCER CELL

SIR,—We agree with Dr Spriggs and Dr Alexander (Sept 17) and we likewise feel that the reports quoted in your leading article of Aug 27 give an exaggerated impression of the incidence of these cells in the peripheral blood

Apart from megakaryocytes, as suggested by Dr Spriggs and Dr Alexander, a variety of other cells[1] may also cause confusion unless one adheres to strict cytological criteria for the diagnosis of malignancy Most of the techniques for cancer-cell isolation so far reported involve incubation, repeated centrifugation, and resuspension of cells for long periods, and the resulting distortion and degenerative changes are easily misinterpreted

Of peripheral blood samples from 30 cancer patients we have been able to find unequivocal evidence of malignancy in only 2 Both of these patients had advanced disseminated carcinoma of the breast Cancer cells are found more commonly in blood from veins directly draining a tumour and perfusion of resected organs bearing malignant neoplasms leads us to believe that cells may be exfoliated into the blood-stream in large numbers It seems probable that few reach the peripheral blood

From our investigations to date it seems unlikely that this phenomenon is of more than academic interest

Postgraduate Medical School,
London, W 12

R A SELLWOOD
J I BURN

SIR,—Your editorial of Aug 27 indirectly noted the difficulty of assessing the viability of circulating cancer cells This is understandable when one considers that the blood sample contains at the most only a few hundred cancer cells Our attempts to grow autoimplants of cancer in volunteer patients have been successful only 15% of the time, even when the cancer-cell suspensions containing over 10 million cells or biopsy specimens weighing 0 5 g were used These implants failed in patients with widespread metastases as well as in those with less advanced diseases Thus, it is doubtful that even autoinjection of cell concentrates can be used for the assay of circulating tumour cells Assays by tissue-culture techniques or by inoculation of animals prepared with cortisone have also been quite successful

There is little doubt that the currently available anti-cancer agents which are very toxic and relatively ineffective against most solid tumours may adversely affect the host This is particularly true if the compounds are given systemically Kondo and others have demonstrated with animal experiments that the adverse effects predominate if the chemotherapeutic action of a compound is insufficient For this reason, we cannot afford general acceptance of new anti-cancer drugs on the basis of popular medical opinion or as the result of inadequate clinical study

We advise general surgeons not to use anti-cancer agents systemically in curable patients Meanwhile, cooperative clinical trials for the evaluation of surgical adjuvant chemotherapy are being carried out

Roswell Park Memorial Institute,
Buffalo, New York

GEORGE E MOORE

THE VERY DEAF CHILD

SIR,—With reference to your annotation of Sept 17, I wish to make the following observations

(1) Both the Association of Non-Maintained Schools for the Deaf and the National College of Teachers of the Deaf are fully aware of the inadequacies of the Board of Education's 1938 system of classifying children with defective hearing, but over the years the terms grades I, IIA, IIB, and III have become accepted as educational, and not medical, categories The grade-III classification was further subdivided into three divisions (*a*), (*b*), and (*c*) to allow for those children with useful residual hearing for vowels, others who were able to respond to loud sounds, and those with no response to auditory stimuli This classification system has never been rigid and any apparent change in a child's use of its residual hearing was fully appreciated

(2) We take exception to the statement "the non-auditory methods in special schools for the deaf preserve the hearing loss of the pupils unchanged" You show a lamentable ignorance of our schools, which are for the most part better equipped with auditory training equipment than any of the pre-school clinics The exploitation of residual hearing is by no means a recent innovation in schools for the deaf As early as 1890 a microphone was, for instance, in use at the Margate school and many schools were equipped with group hearing-aids before the late war

(3) Teachers of the deaf have always been willing to make use of any apparatus which would help to improve the achievement of deaf children At the same time they are fully aware of the limitations, even of the best available electronic hearing-aid apparatus when used with children born profoundly deaf or those who become deaf before speech is established

In a recent investigation into the listening and lip-reading abilities of a group of severely deaf children and their capacity for combining lip-reading with aided listening, the following results were obtained

	No of children	*Mean decibel loss*	*Listening % score*	*Lip-reading % score*	*Combining % score*
Hearing loss greater than 94 decibels	25	101 3	6 5	57 4	64 8
Hearing loss less than 94 decibels	25	76 2	43 8	64·9	60 8

From these scores it will be noted there is a significant difference between the means of the two groups in their ability to combine lip-reading and listening With both groups, however, there is still a considerable gap before it is possible to obtain full comprehension and their learning process will require the highly specialised and skilled art of the teacher of the deaf The education of these children will suffer, as there is ample evidence to show some of them are doing, by being placed in ordinary schools without the full-time supervision of a fully qualified experienced teacher of the deaf, in the pious hope that by rubbing shoulders with hearing children they acquire speech automatically Many schools for the deaf have admitted these children at a later age after the harm has been done, and the resolution of the Association of Non-Maintained Schools for the Deaf was sent to you in the hope that profoundly deaf children should not be sacrificed on the altar of normality as expounded by the fanatics who know little about the educational handicap of deafness

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[1] Rebuck, J W *J Lab clin Med* 1947, 32, 660

Royal Cross School,
Preston

PETER GASKILL
Press Relations Officer,
National College of Teachers of the Deaf

SMOKING BY ADOLESCENTS

SIR,—There is a short and simple answer to the last sentence of Dr Fisher's letter of Sept 24 if a personal experience is any guide 75% of the doctors of my acquaintance smoke cigarettes If this sample is any indication of the percentage of the profession as a whole it would indicate that we have no interest in telling the Government to stop cigarette advertising, whether we believe in the dangerous effects of smoking or not The profession has no cohesion and the Government no morals, and 25% of doctors objecting would have no power to curb the Exchequer's grasp after money

Incidentally, may I comment that the logic of Dr Fisher's second paragraph and the bulk of the last seems to me to be aulty? If there is one country in the world where liberty is bused it is our own, and that is a fault as venal as its denial f it is right to discourage morphine addiction, suicide, and marriage under the age of 16 (and why 16?), it is right also to prevent youth from exposing itself to a risk that may in later life destroy life

Lastly, Sir, it seems a pity that when so much is done today o strengthen the concept of preventive medicine such scant attention is paid to the vicious habit of cigarette addiction Even though 75% of smoking doctors should believe in the carcinogenic properties of cigarettes it could not lie in their mouths to advise the public against them without the unanswerable questions being asked "Well, why do you do it yourself then?"

It is long past the time when the profession should have taken a firm stand against the cigarette and its manufacturers and stopped hiding behind a gigantic packet of coffin nails

Folkestone.

B G EDELSTON

OBSTETRIC FLYING-SQUADS

SIR,—I am writing in delighted support of the letter of Oct. 1 from Dr Walker, who condemns those "obstetricians who persist in the obviously false belief that there is some magical security in hospital buildings" There is safety and security in the men and women who work in those hospitals but the hospitals themselves are a mild source of danger The skill, knowledge, and experience of senior obstetricians is what makes hospital confinement safe If those obstetricians decide, for whatever reason, that they will not move out of their hospital buildings then the safest place for a woman to have her baby is in those hospitals in spite of the dangers thereby incurred If, on the other hand, those obstetricians are prepared to go out with their equipment and apply their skill in the patients' homes the dangers of hospital confinement are eliminated and the greatest degree of safety is achieved

Several excuses are given why skilled obstetricians will not move from their hospitals The commonest is that there are "facilities" in hospital that cannot be provided outside I know of no "facility" that cannot be transported Another is that time is saved in an emergency such as hæmorrhage. I could give numerous examples of transfusion being started fifteen and twenty miles away in shorter time than it takes to get a sleepy resident into action Many senior obstetricians cannot act in a home as they would in their hospital because, never having experienced anything other than hospital work, they feel uncomfortable, unhappy, and indecisive without their familiars around them The real reason for the false propaganda to urge women to go to hospital is economic It is somewhat wasteful of the time, effort, and energy of the senior obstetricians to use them except amongst a congregation of puerparæ I would not go so far as Dr Walker and say that these obstetricians are lazy-minded in sticking to their hospitals Economically they are being sensible The patient will be safer wherever these men are applying their skill but if the patient goes into hospital she has added slight dangers, such as a threefold likelihood of developing mastitis

I hope, Sir, that you notice that I have not specified consultant obstetricians Not all skilled and experienced obstetricians are consultants and not all consultants are skilful obstetricians

Newcastle upon Tyne

FRANK STABLER

MORTALITY DUE TO BLOOD-TRANSFUSION

SIR,—Statistics can mislead, as Dr Harris Joseph emphasises in his letter of Sept 24, in which he sets out to clarify the position of mortality-rates in present blood-transfusion therapy There is always the danger that outdated figures become perpetuated in the literature regardless of the changes and improvements of more recent times which should modify them

However inaccurate such figures may be, they are far less misleading than those based on information given to the Registrar-General by way of death certificates Many deaths due to blood-transfusion are not immediately apparent and many are obscured by the underlying condition for which the transfusion is given—e g, the connection between blood-transfusion and delayed cirrhosis following serum hepatitis is easily lost because of the prolonged time-lag Although the estimate of 1 death to 1000 to 3000 transfusions[1] may not relate to present practice, it is probably much nearer the truth than the estimate given by Dr Joseph of 1 death to 250,000 to 350,000 Incidentally, Dr Joseph wrongly assumes that each transfusion is of one unit only

In 1959 about 700,000 units (bottles) of blood were issued to hospitals in England and Wales Taking the average of 2 bottles per transfusion, this means about 350,000 persons were transfused and, according to Dr Joseph, there would only be 1 or at the most 2 deaths from this number of transfusions The absurdity of this will be apparent to all those concerned with this branch of medicine

Dr Joseph quotes 234 deaths in 6 million transfusions in U S A for the two years 1957 and 1958 and concludes that there was 1 death in every 256,000 transfusions Actually, he has misplaced a decimal point and his figures should read 1 in 25,600 If this figure is accepted, then he has shown a mortality-rate ten times greater in the U S A than in this country!

South London Transfusion Centre,
Sutton, Surrey

R A ZEITLIN

SIR,—Dr Harris Joseph says that in the United States there were 234 deaths after nearly 6 million blood-transfusions in two years, or a mortality of 1 in 256,000 If, however, the figure for the deaths and the number of transfusions is correct, the mortality is 1 in 25,600 I hope Dr Harris Joseph will say which figure is correct

London, W 1

GEORGE GRAHAM

SIR,—Dr Harris Joseph's inquiries into the origin of the figure for blood-transfusion mortality quoted by Guynn and Reynolds are of interest, and the fact that the figures date from 1917 renders them invalid as regards modern transfusion.

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[1] Graham-Stewart, C. W *Lancet*, Aug 20, 1960, p 421

Firstly, he states that the mortality of blood-transfusion, according to the Registrar General's statistics, is in the region of 1 in 350,000 rather than 1 in 1000–3000 Unfortunately he is replacing one unsatisfactory figure with another equally unsatisfactory

Similar inquiries have been made into the origin of the figures which Dr Joseph has compiled from the Registrar General's statistical review of England and Wales, 1951–58 Under the heading " Adverse reactions to injections, infusions and transfusions for therapeutic purposes " there are 8 deaths over the five-year period This category is not broken down any further and I have been unable to find any figures giving the mortality of blood-transfusion These figures are therefore valueless

Secondly, as I have not had access to the United States Bureau of Vital Statistics figures for 1957 and 1958, I can but quote the figures given by Dr Joseph—234 deaths from 6,000,000 transfusions The mortality is 1 in 25,600 and not 1 in 256,000 There is therefore no correlation between the figure not applicable to blood-transfusion compiled from the Registrar General's statistics and an incorrect figure taken from the Bureau of Vital Statistics

I agree that to quote a mortality figure of 1 in 1000–3000 in a discussion condemning one-pint transfusions is wrong, but surely the crux of the matter is, What is the meaning of the term blood-transfusion mortality? Does it apply solely to patients dying directly as a result of a mismatched transfusion in which the patient receives the wrong blood or does it include those dying of complications attributable to blood-transfusion?

The mortality of small planned transfusions must be very low Death may be due to giving incompatible blood, or, rarely, virus hepatitis But what of the mortality of large transfusions, often given in difficult conditions, where the alternative is death or blood replacement? Death may be directly attributable to (1) over-transfusion, (2) air-embolus, (3) potassium intoxication, (4) phlebitis, leading to septicæmia, or (5) unexplained bleeding following massive replacement

Is death in these cases recorded as being due to blood-transfusion in the Registrar General's figures? It is more likely that death is certified as being due to renal failure, pulmonary œdema, &c, rather than primarily due to transfusion The principal reason why the figures given by Guynn and Reynolds are quoted is that there are no satisfactory alternative figures

Lest it should be thought that the above list is of theoretical causes of death, I should like to say that I have personal knowledge of deaths due to three of them

St Thomas's Hospital,
London, S E 1

C W GRAHAM-STEWART

SIDE-EFFECTS OF LIBRIUM

SIR,—Dr Ingram and Dr Timbury (Oct 1) report on some unpleasant symptoms seen in their patients given methaminodiazepoxide ('Librium') They used it in 15 patients and noted drowsiness, apathy, dizziness, constipation, inability to continue working, irritability, and aggressiveness The patients did not seem to be helped much, and with these results in mind they wisely suggest " circumspection and scepticism "

We have, however, used librium in approximately 160 patients, 99 of these were anxiety neurotics selected for a double-blind trial In general we used 20 mg twice a day On this dose 18%, of our patients complained of slight drowsiness None had to stop working for this reason Ataxia was also a significantly commoner complaint in older patients on the active substance than in those receiving the placebo Nevertheless, 1 patient demanded that the placebo should be reduced, and only 1 other patient appeared to have objective evidence of ataxia The latter patient refused to continue taking librium

A patient took 150 mg at one dose, and we have personal experience of taking up 100 mg on two occasions in the same day These doses produced moderate drowsiness and slight ataxia Other symptoms produced during the trial period of one month occurred more commonly while the placebo was being taken

We are submitting our study for publication elsewhere Our results indicate, however, that librium affords symptomatic relief in anxiety states, and they also suggest that it is not a dangerous substance

Whiteley Wood Clinic,
Sheffield

F A JENNER
R J KERRY
D PARKIN

BUS-DRIVERS WITH ISCHÆMIC HEART-DISEASE

SIR,—Dr Goldsborough, in his interesting article of Sept 24 on the value of nicotinic acid in ischæmic heart-disease, quotes seven illustrative cases

Case 2 " collapsed at the wheel July, 1949 ", had " a severe attack of coronary thrombosis " in 1951, and in 1957 " his angina again returned fairly severely " His electrocardiogram " showed a grossly abnormal pattern " Yet " he continues his bus-driving " He must now be 56 years old

Case 3 developed angina of effort in 1950, had a coronary thrombosis in 1955, and the E C G demonstrated " unequivocal infarction " Yet " he has been driving continuously since "

We must accept the fact that these patients are conscientious about treatment But a quarter of the 24 patients with coronary thrombosis died, and 2 died suddenly despite symptomatic relief In this context may I ask if it is wise or safe to allow the two cases quoted to continue to drive public-service vehicles? Do they have to undergo any medical examination at work? I would have thought, in the heart of the West Riding, that it would have been expedient to obtain safer work

Stanley,
Co Durham

R McL ARCHIBALD

HYDROCORTISONE BY INHALATION

SIR,—We were interested in the paper of Aug 20 by Dr Langlands and Dr McNeill on the treatment of asthmatics with ærosol hydrocortisone In autumn, 1959, we carried out a similar investigation using the cross-over blind-trial technique in 9 asthmatic children These children were given hydrocortisone inhalations for one month and similar " placebo " inhalations for a month

The dosage and methods were slightly different from those of Dr Langlands and Dr McNeill We prescribed a dose which would not be effective if taken by mouth—i e, three puffs q d s of 'Medihaler-cort', equal to 18 mg of hydrocortisone acetate daily The measurement of ventilatory capacity we used was similar to that used by Dr Langlands and Dr McNeill—the indirect maximum breathing capacity[1] or E F R[4] which was recorded twice weekly before and after the inhalation of 1/1000 adrenaline As regards symptomatic change, all patients attending the department keep their own day-to-day diary about relevant symptoms

The problem of assessing any form of therapy in asthma is beset with many difficulties in both adults and children For instance, there is often a wide seasonal variation which even in a given individual is not always constant from year to year The 9 children referred to above were selected from a group under long-term investigation and had been under detailed weekly observation for periods ranging from one to five years before the trial From the careful study of the yearly charts embodying the detailed objective and subjective data there was no striking evidence of improvement of the breathing defect or asthmatic symptoms during treatment with the active aerosol, such as is sometimes seen with oral steroids in effective dosage[2,3]

None of the 9 children were appreciably worse with either form of inhalation 5 out of 9 children showed some improvement in their E F R[4] while having the inhalations, but the was little difference between hydrocortisone and placebo 1 child was better on hydrocortisone but 2 were better on placebo The remaining child showed no response to either On the basis of these objective findings in children and other studies on adult asthmatics we would agree with the findings of Morrison Smith [4] and Dr Langlands and Dr McNeill

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[1] Kennedy, M C S *Thorax*, 1953, 8, 73
[2] Kennedy, M C S *Acta allergol* 1960, 15, 187
[3] Thursby Pelham, D C, Kennedy, M C S *Brit med J* 1958, i, [illegible]

There was no marked symptomatic change in 9 children while receiving the inhalations Comparing the symptoms on hydrocortisone inhalations and on placebo, 2 were better on the hydrocortisone and 2 were better on the placebo, the remainder showed little difference. Although our findings agree with the reports that certain individuals are symptomatically better whilst having hydrocortisone by inhalation,[5] [6] in our patients we are not convinced that this improvement results from the treatment.

Thus we were unable to substantiate our hope that the smaller doses given by inhalation would be effective without the undesirable side-effects that are sometimes associated with systemic therapy Larger doses given locally by inhalation may well be effective, but if so one may only be achieving a systemic effect from local absorption In fact we have patients with severe asthma and eczema whose breathing defect as well as their eczema has been completely suppressed by the liberal application of hydrocortisone cream

Department of Respiratory Physiology,
City General Hospital,
Stoke-on-Trent.

M C S KENNEDY
D C THURSBY-PELHAM

SPORTS MEDICINE

SIR,—I was interested to learn Dr Troup's view (Sept. 24) on this subject, appearing at a time to coincide with the disappointing performances of British athletes in Rome and the report of Sir John Wolfenden's committee I agree that research into methods of training is required, but adequate facilities for such training must exist.

I cannot agree with his second paragraph As long ago as 1948, and again in 1954, Cyriax [7] [8] described in detail a method of restoring sprains of ligaments, tendons, and muscles to full function in a very short time Since hydrocortisone became available relief can be achieved even more rapidly in some cases The treatment, whether by deep friction or injection, requires an exact localising diagnosis, for even correct treatment given to the wrong spot will fail

I have taken a special interest in treating athletes and ballet dancers on these lines, described further by Cyriax [9] in 1958, and have dealt with some in the Olympic class, after they have failed to recover from an injury in spite of physiotherapy and hydrocortisone injections They have been able to return to full training after a few treatments given to the precise site of the injury

A diagnosis may be impossible to reach in a highly trained athlete after he has been resting He must make the physical effort which produces the pain and be re-examined immediately At St. Thomas's Hospital, athletes have run up and down the terrace, maybe for two miles, before symptoms appeared. Re-examination then disclosed the tissue at fault, so that correct treatment could be given and normal function of the structure restored

It is my experience that athletes tend to depend on the club masseurs for diagnosis and treatment and call for aid from the medical profession only when they have failed. This is wrong A medical opinion of the exact diagnosis and treatment required is the first essential—for example, the most acute ligamentous strain of the knee in a footballer, if seen in the first twenty-four hours, can be cured in seven to ten days The more recent the injury, the more rapid is the cure By contrast, many injuries recover by themselves in the end with rest, but break down again when put to the test, chronic sprain resulting The lesion must be properly treated until full function is restored.

London, W 1

R. BARBOR.

PERCHANCE TO DREAM

SIR,—In your leader last week, discussing Dement's work on dreams, you state that he had observed that dreams were accompanied by rapid synchronous eye movements

Unfortunately he has observed nothing of the sort. What he has observed is that during a night's sleep there are periods of light sleep during which there are rapid synchronous eye movements, if a person is awakened during one of these periods Dement found that he is much more likely to *remember* a dream than if awakened during deep sleep Dement, however, has produced no evidence to show that people do not have dreams during deep sleep, they may simply not be able to remember them and so report them.

Therefore, before psychologists set forth on a series of experiments on the lines suggested by Dement it is as well to remember that one of the basic hypotheses of these experiments is unproven

London, N 21

J M HEATON

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Dr R M Acheson (Sept 24) repeats again the thesis that there is a separate ætiology for coronary thrombosis and atheroma This was propounded by Morris in 1951 [1] and stated more succinctly in 1958 [2] One would conclude from these articles and from Dr Acheson's letter that coronary disease in the younger age-groups is a different one from that occurring in patients from 60 years of age onwards Many of us who actually handle morbid material find this conclusion difficult to accept The contribution by Crawford to the Royal College of Physicians symposium [3] on occlusive heart-disease expresses our doubts, and further work at present being done in this laboratory is providing confirmatory support

There seems to be a difference of opinion between laboratory workers and theorists which still needs to be resolved

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A P PRIOR.

ASSESSMENT OF HEPATIC SIZE, SHAPE, AND CONTENT

SIR,—Your annotation of Oct 1 might, I think, have mentioned the simple manœuvre of placing the hand, preferably gloved, directly on the organ Whilst not infallible, it is remarkable what reliable negative and positive findings it can reveal I am surprised that it is not used more often.

On more than one occasion a man has been spared a useless pulmonary resection for cancer by performing a preliminary laparotomy Conversely, I have also enabled a patient to undergo a successful operation by first demonstrating that the considerably enlarged liver was not the site of obvious metastases

Why must we continue to guess when it takes little more than ten minutes to establish the correct state of affairs fairly confidently, and does not significantly add to the postoperative distress? Early and deeply placed metastases may of course be missed

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[4] Morrison Smith, J *Lancet*, 1958, ii, 1248
[5] Brockbank W, Pengelly, C *ibid* i, 187
[6] Helm, W H., Heyworth, F *Brit med J* 1958, ii, 768
[7] Cyriax, J H. Rheumatism and Soft Tissue Lesions. London, 1948
[8] Cyriax, J H Orthopædic Medicine. London, 1954
[9] Cyriax, J H. *Medicina Sportiva*, July, 1958

[1] Morris, J N *Lancet*, 1951, i, 1
[2] Morris, J N, Crawford, M D *Brit med J* 1958, ii, 1485
[3] Crawford, T Pathogenesis and Treatment of Occlusive Arterial Disease. London, 1959

If it is felt that the additional pain may restrict pulmonary ventilation unduly, then the postoperative epidural anæsthesia will relieve the pain of both the thoracic and abdominal wounds

Short of a laparotomy, the radiologist's use of a pneumoperitoneum[1] has something to commend it in the occasional demonstration of metastases in the liver

The Churchill Hospital,
Headington, Oxford
C Grimshaw

RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

Sir,—I was very interested in the article of Oct 1 by Dr Pryer and his colleagues because I had precisely the same experience

The operation was a craniotomy and all the procedure of positioning the patient and towelling up was completed, but fortunately no incision had been made On discovering respiratory obstruction I asked to remove the tube the surgeon was most cooperative and we restored the patient to a supine position and reintubated with no untoward effects other than repositioning, retowelling, &c

However much the surgeon is inconvenienced it seems that the answer is to remove a doubtful tube immediately, insert an airway, ventilate, and reintubate The offending tube was found to inflate unevenly, and, as in Dr Pryer's case, a protrusion had developed behind the bevel of the tube

London, W 2
Margaret Joad

Medicine and the Law

Private Treatment by Part-time Consultants

In principle the position of a part-time consultant under the National Health Service is simple enough he is entitled to take private-fee patients, but he is never entitled to take fees from N H S patients or to admit private patients in that capacity to ordinary hospital beds In practice, however, he may find himself in a position of some delicacy where (as he is entitled to do) he discusses with an N H S patient the possibility of private treatment The dangers involved are illustrated by the report of an inquiry released by the Minister of Health into allegations of irregularities in charging patients in the Shrewsbury area Five allegations were brought against Mr X, a part-time consultant, that he accepted money for procuring hospital beds

The inquiry was ordered by the Minister under section 70 of the National Health Service Act, 1946, and was held in private It was conducted by a committee consisting of Mr G G Baker, Q C, and Mr Victor Lack, F R C O G, with a legal secretary Counsel instructed by the Ministry acted in effect as counsel for the prosecution Mr X and a hospital sister were legally represented, and evidence was given by the patients concerned and by other persons involved The report does not indicate whether the witnesses were on oath, but it seems probable from the obvious care with which the inquiry was conducted that use was made of the power under section 70 to require evidence to be given on oath

In view of the gravity of the allegations and the serious consequences which could have ensued, the committee considered the facts and reached their conclusions, not on a balance of probabilities, but on the basis that the allegations ought to be proved beyond reasonable doub On this footing, they found in four cases that the allegatio was not proved, and in the fifth case that there was n evidence

THE GENERAL FACTS

Mr X was at all material times a part-time consultant a certain hospital (" the hospital "), being responsible for th treatment of patients in the maternity and gynæcologic wards He was ultimately responsible for admissions, thoug he had never checked the system of bookings Primigravid and cases with complications were generally accepted. Appar ently there was no great shortage of beds, but difficulties di arise from time to time The hospital is not one in which th Minister has set aside accommodation for paying patient under section 5 of the Act of 1946, all admitted patients ar consequently non-paying N H S patients

There is in the town an antenatal clinic which the patien attends with a letter from her doctor During the relevan period until July, 1959, the patient would first see a woma receptionist, who would open the letter (unless it was marke " personal ") and would, if the patient qualified for a bed book her either with or without reference to Sister C, th sister in charge of the maternity ward at the hospital, wh attended at the clinic

Mr X also attended the clinic with one or more house-surgeons If a patient was booked by the receptionist, a chart would be made out and she would be referred, through Sister C, for examination by one of the doctors If there was a query on the letter or if it was " personal ", the patient would be referred direct to a doctor Sister C was directly responsible for the bookings, and kept a record book in her office at the hospital In it she would put names received (*a*) from the receptionist at the clinic, (*b*) from charts she had herself made out, and (*c*) of patients she had been told to book by Mr X, who sometimes made out charts elsewhere than at the clinic Approximately 70 bookings were accepted for any month—60 at the clinic and 10 kept for emergency If Sister C was getting near the danger limit she would tell the receptionist and the doctors to " go easy " It would depend on how far ahead bookings were being made, thus, she would draw the line in the forties in February for admittances in August

The committee conclude that the arrangements for the admission of maternity and gynæcological cases are, or at any rate were, unsatisfactory Bookings were made by the receptionist, Sister C, or the medical staff, and as a result confusion could occur Added to this, Mr X exercised no real control over booking procedure

CASE OF MRS A

Mrs A was pregnant with her first child At the clinic her doctor's letter was put on Mr X's table—an indication that the bed state at the hospital was fully booked or at least had reached the point at which there might be difficulties Otherwise, being primigravida, Mrs A would have been booked by the receptionist or Sister C

Mrs A then saw Mr X and asked him about the possibility of being a private patient He mentioned a fee of 25 guineas and a further 15 guineas for private antenatal care The committee are satisfied that Mrs A left under the impression that, if she became Mr X's private patient at a fee of 25 guineas, he would then arrange for her to have her baby in the hospital but that otherwise she would be unable to get a bed there. But the committee are not satisfied that that is what he intended to convey He said in evidence " I said if she wanted to attend me privately she could do so, but I could not guarantee her a bed. I would have to see if there was some reason for her admission " The committee consider that this might well have given a false impression to a patient, particularly if (as was suggested) she was told to keep it in the family because of the danger of misunderstanding " Mr X has nobody but himself to blame for his subsequent difficulties because we think it was his duty to check the bookings and to make this position clear to Mrs A beyond peradventure, preferably in writing "

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[1] Lumsden, K., Truelove S C. *Brit J Radiol* 1957, 30, 516

After an interview with the secretary of the hospital management committee Mrs A made an appointment to see Mr X at his house She went with her mother (as she admitted) with the deliberate intention of trapping him, she and her mother were *determined to get the signing of a cheque linked to the* promise of a bed at the hospital. The committee infer that this procedure was instigated by the secretary of the management committee, and comment "In our view it was unfortunate that these two ladies should have been permitted to embark on this effort to trap Mr X, because they went with the unshakeable impression that Mrs A as a private patient, but not otherwise, could get a bed and they were determined to secure further support for this view   Such an approach, even if made by impartial and trained investigators, is open to the criticism that everything that followed was coloured by the object to be attained."

At this interview Mr X accepted from the mother a cheque for 25 guineas This was more than the agreed fee for antenatal care, but Mr X said that he thought that the mother was being generous He also examined Mrs A and considered that there was sufficient justification for admitting her to hospital The committee say "Little further justification would be required for accepting a primigravida case even if the bed state was critical and it was sufficient that Mrs A appeared to have a narrow pelvis "

When Mrs A failed to keep further appointments, Mr X sent her a cheque for 15 guineas (being the fee less a deduction for visits already made and appointments not kept) and told her that the hospital booking stood but might be cancelled if she did not attend the clinic for antenatal examinations She was delivered in another hospital by a Mr Z

Having considered all the evidence and having regard, in particular to the trap, to the possibility of an initial mistake, and to the demeanour of the witnesses, the committee find that the allegation that Mr X asked for and accepted the sum of 25 guineas ostensibly for antenatal treatment but in fact for procuring a bed at the hospital is not proved.

SOME POINTS OF MEDICAL ETHICS

The report then deals with the other four cases, and Mr Lack adds some comments on points of medical ethics raised by the inquiry

(1) When a patient is referred to a part-time consultant at an N.H.S antenatal clinic, he should decide whether she is to come into hospital for her confinement. If there is any difficulty about arranging admission, the patient should be examined before being told that there are no beds available She may have some abnormality which justifies her admission, and this is the time and place to discover it. There are beds reserved for such cases If the patient is refused a bed at the clinic and later given one after a private consultation, there is scope for misunderstanding

(2) If a patient is first seen by a consultant at an N H S clinic, she should not be seen by him privately unless she is later sent to him by her doctor

(3) A patient may find it difficult to attend the clinic and may ask the consultant to carry out the antenatal work privately There is no objection to this provided the patient is booked for a bed before the arrangement starts As a precaution, the patient should be asked to sign a form

(4) The patient may in the first instance have been sent by her doctor to see the consultant privately with a view to admission to hospital In such cases the consultant should decide whether the patient is suitable for admission in accordance with the rules of the hospital concerned. He may legitimately charge a consultation fee

The Minister of Health has announced that he is considering whether further guidance to hospital boards is necessary in view of Mr Lack's comments

Obituary

ARTHUR ALEXANDER GEMMELL

Kt, M.C., M.D Cantab, F R.C S E, F.R.C O G, Hon. M.M S.A.

THE qualities of integrity, conscientiousness, and courtesy which won Sir Arthur Gemmell his special place in Liverpool and the Palatinate also won him an honoured place at the council table of the Royal College of Obstetricians and Gynæcologists and as a welcome visitor to many Commonwealth teaching centres It will not be an easy place to fill and the news of his death on Sept 24, which we announced last week, will be widely regretted.

Camera Press

He was born in 1892, the eldest son of Dr John E. Gemmell who was one of the first specialists in obstetrics and gynæcology in the North of England. From Uppingham Arthur Gemmell went to King's College, Cambridge, and later to Liverpool University But his studies were interrupted by the 1914–18 war during which he served as a combatant in the Liverpool Scottish Regiment in France and with the Queen's Own Cameron Highlanders in Salonika. He was awarded the Military Cross of Greece as well as of his own country He found army life so much to his taste that he seriously considered making it his profession In the end he chose medicine, and he returned to Liverpool to finish his clinical training, graduating in 1922, but he retained his interest in military medicine and history, and as a Territorial he commanded the Liverpool Scottish Regiment in the '20s

After graduating he settled in Liverpool and during his first formative years in his specialty he was happily associated with such distinguished gynæcologists as Briggs, Leith Murray, Leyland Robinson, and Blair Bell. His first appointments were with the old Shaw Street Hospital and the Samaritan Hospital for Women in Liverpool, and when they joined he helped to plan the new Women's Hospital and in due course became its senior surgeon. There and at the Liverpool Maternity Hospital and David Lewis Northern Hospital he carried out most of his clinical work, yet he found time to visit Cheshire and North Wales hospitals In this part of his work he was particularly successful, and many of his colleagues from the Liverpool region will endorse N E L's words

"Sir Arthur was always quite willing to come to Southport, even after the long hours of his own work, and to give me his advice. It was encouraging when he supported my views and treatment, and if he suggested changes this was expressed with the most delicate consideration for the feelings of junior colleagues When the health service was started Sir Arthur was appointed senior consulting obstetrician and gynæcologist in this district, and I became his junior During this time I learnt to admire the gentle way in which he exercised his control, without creating any feeling that Liverpool was dominating the smaller areas "

Gemmell served his own school as a clinical lecturer in the department of obstetrics and gynæcology, and he examined for Cambridge University, the Conjoint Board, and the Royal College of Midwives He also contributed much to medicine in the North of England by his support of its lively local societies, such as the North of England Obstetrical and Gynæcological Society and the Liverpool Medical Institution, over both of which he presided After he retired in 1957 he was even more generous with his time and he often said that he was busier than ever He served on university committees, the United Hospital Board, the Regional Hospital Board, and the gynæcological advisory committee, as well as on many national committees associated with the health service

This record of local service steadily won wider recognition and he visited Australia, New Zealand, and the United States as lecturer and an official delegate But his chief interest was of course the young college of his specialty, which he served from its inception, and the most appropriate recognition of his work was his election as its president. Reviewing his association with the college, I J writes

"Sir Arthur Gemmell's service to the College began in 1935 and continued without a break until his death He always regarded it as a privilege to serve the College of which his father was a foundation fellow and he a foundation member His enthusiasm never flagged, indeed he applied himself to every undertaking with a vigour which astounded those of us who were his colleagues At one time or another he was a member of every standing committee and with the wide experience gained in this way during the College's formative years and his meticulous attention to detail, it was fitting that he should be elected to the responsible office of honorary treasurer in 1946 He accepted this office knowing that it was no sinecure, the need for a new building had been agreed and the money to pay for it had to be raised. Sir Arthur tackled this project with characteristic diligence and launched the first appeal for the building fund in 1947, and it is in no small measure due to him that the new building was completed this year

"He regarded his election to the presidency in 1952 as a great honour, but also a great responsibility He threw himself wholeheartedly into his arduous job without thought for himself and with his tremendous sense of duty attended to matters large and small with the same careful attention to detail I would often receive carefully corrected drafts of letters in his own hand

"But much of the pleasure he might have had was denied him by the ill-health of his wife, though he did not let this interfere with the duties he had undertaken By sheer determination he fulfilled all his engagements, many times spending his nights in the train between Liverpool and London so as to be with her In 1954 he accepted the invitation to open the new College house of the Australian Regional Council and gave the first Arthur Wilson memorial lecture, though he undertook this duty in the midst of great personal anxiety, and accomplished the visit in the minimum of time

"We were indeed disappointed that he was not well enough to attend the opening of the new College in Regent's Park, but with characteristic generosity he sent an additional cheque to the endowment fund for the amount he would have spent on attending the ceremony with his guests We shall miss him as a loyal friend and a wise counsellor"

"He will always be remembered for his loyalty and devotion to the College," writes Dame Hilda Lloyd "During his eight years as hon treasurer and his subsequent presidency he gave of his very best and guided the College with skill, tact, and diplomacy Unassuming and modest, he was ever mindful of the welfare of others"

But, despite his travels, it was to Liverpool Gemmell always returned, and the final tribute to him as a man rightly rests with J H, one of his own students

"There can have been few doctors as conscientious as Arthur Gemmell. Whether he was caring for patients or attending a committee he always gave the matter his whole attention and time. All his patients always had the impression that they were the only patient that mattered, and so full purpose was Arthur Gemmell that this was undoubtedly tru In administration he had, as a result of his regard for detai a masterly grasp of all sides of the problem before any meetin was held He did not, however, come with preconceived notion and would always listen to all arguments courteously an carefully As one of his students I well remember his carefu teaching but still more his unfailing consideration of patient As his junior consultant at three hospitals I found how helpfu and considerate he was A friendly word of advice given quietl often made a big difference to one's own personal decisions As Francis Bacon says, 'If a man be gracious and courteou to strangers it shows he is a citizen of the world' I feel tha the fact that Sir Arthur Gemmell was recognised all over the world as Arthur makes him one of its citizens"

Sir Arthur Gemmell is survived by a son and tw daughters

ALEXANDER MILLS KENNEDY

M.D Glasg, F R C P

Dr Alexander Mills Kennedy, emeritus professor of medicine in the University of Wales, died at Cardiff on Sept 24

He was educated at Allan Glen's School and the University of Glasgow, qualifying in 1908 His postgraduate training was exceptionally wide, and his profound knowledge of clinical medicine owed much to his background of pathology and bacteriology In 1912 he took the degree of M.D with the highest honours At this time he was working on histological changes in the cardiac conducting system, and between 1910 and 1914 he published, with John Cowan, Fleming, and Wardrop Griffith, some beautiful accounts of such changes in cardiac arrhythmias Another important paper was his study of renal cortical necrosis He always maintained his interest in the cardiovascular system, and he was a member of the Cardiac Club and later of the Cardiac Society

In his years in Glasgow he was in turn resident physician at the Royal Infirmary, assistant medical electrician (in charge of the electrographic department), senior assistant pathologist, assistant physician, senior assistant to the Muirhead professor of medicine, senior assistant to the professor of pathology, and director of the research department at the Royal Maternity and Women's Hospital, In 1914 he joined the British Red Cross, and from 1915 onwards he served in the R.A.M C. as pathologist and was mentioned in despatches His work in the Army brought him into contact with Worster-Drought, and after the war they published their monograph on cerebrospinal fever On his return to Glasgow Kennedy organised postgraduate teaching for many returning from the war

Soon after the end of the war the Royal Commission on medical education in Wales recommended that the preclinical school at Cardiff should be made into a full school, and that there should be professorial units in the main clinical subjects The findings and recommendations of the Royal Commission were widely welcomed in Wales, but, when it came to making the appointments, personal disappointment and bitterness arose In 1921, when Kennedy came to Cardiff as the first professor of medicine and director of the professorial medical unit, no preparations for teaching the students had been made He spent his first weeks in a frigidly hostile atmosphere making what arrangements he could to find space and facilities to start teaching The troubles in the medical school, which came to a head in 1928, naturally troubled him a good deal, but a satisfactory solution was finally reached, and, after a new constitution of the school was drawn up in 1931, he worked for many years with enjoyment and zest Apart from occasional articles on clinical subjects, his main publications were a small book on case-taking for students, and an admirable *Parasitology for*

Medical Students which contained a colour plate of the forms of malarial parasites made from his own water-colours He retired in 1950

A colleague writes

"Despite the unhappiness of his start in Cardiff, Kennedy set to work energetically to develop a university department. He realised at once that it would be essential for progress in medicine and in teaching to have laboratory facilities for students and for research in close physical relation with wards, and in 1928, through the generosity of the Rockefeller Foundation, there was erected to his design the magnificent five-floor block which still accommodates the medical unit and which has set the pattern for physical integration between medical school and teaching hospital He gave most of his time in these years to the teaching of students, and throughout his tenure of the chair he felt his prime duty was the teaching of principles to junior students He was an outstanding clinician who, though he had a wide laboratory background, in teaching always emphasised the first importance of history-taking and of meticulous physical examination, and in both these skills he was himself an outstanding expert His patients regarded him with great affection and had the most complete faith in him, and this was hardly surprising since not only did he spend much time in the wards with them, but his interest was in every patient and he spent as much, if not more, time with those with peptic ulcer and diabetes, for example, as with those with rarer conditions Although initially drawn to cardiovascular problems, from the time he came to Cardiff he interested himself in the whole field of medicine. He would spend many hours on the accurate localisation of a spinal-cord tumour, and nothing delighted him more than the surgical success of his colleague Lambert Rogers in a series of these patients Kennedy's success in therapy equalled his care in diagnosis, and he kept abreast of changing concepts and had a flair for deciding early which new treatment had real promise while rejecting in no uncertain terms ill-based novelties From his father, an analytical chemist who was a manufacturer of heavy oils and greases, he derived a great interest in industrial processes and the origins of industrial materials, which he often used in his clinical work.

"Kennedy was a man of wide culture, interested in fine editions and general literature, and having a great knowledge of Scottish history and antiquarianism In his youth he had been a talented performer on the piano, organ, and mandolin, and his love of painting continued until in retirement he turned again to water-colours, in this medium he had more than a simple talent. His considerable collection of etchings and water-colours included fine example of the works of Zorn, D Y Cameron, Muirhead Bone, and Russell Flint. When he retired his students presented him with a gold half-hunter, and it was only then and in later meetings of the Old Students' Association that he seemed to realise how much his single-minded devotion to their interests and his intolerance of intrigue and place-seeking had endeared him to many generations of those he had taught"

THOMAS HERBERT JOHN CHAPMAN GOODWIN

K.C.B, K C.M.G, D S O, Hon D Sc. Oxon, F R.C S

Lieut.-General Sir John Goodwin, director-general of Army Medical Services from 1918 to 1923 and a former governor of Queensland, died on Sept 29 at the age of 89

He was born at Kandy in Ceylon where his father, Surgeon-Major John Goodwin, was serving, but he was sent to the family home at Newton Abbot in Devon for his education. He qualified from St. Mary's Hospital in 1892 and the following year entered the Army Medical Service. He served with the Mohmand Field Force on the North West Frontier and won the D.S.O at the battle of Shabkadar in 1897

When war started in 1914 he was in command of a field ambulance attached to the Cavalry Division and took part in the retreat from Mons Soon afterwards he was appointed A.D M.S of the 2nd Cavalry Division and went through the battles of Ypres and the fighting on the Somme In 1917 he was appointed assistant director-general of medical services and visited the United States as one of Mr Balfour's mission His practical knowledge of the medical needs of the Army impressed his American colleagues, and when, on America's entry into the war, American Service doctors came to this country Goodwin had already made many friends among them He was appointed C M G in 1915 and C B in 1918 for his war services

In 1918 he succeeded Sir Alfred Keogh as director-general of Army Medical Services In 1927, four years after he retired from the Army, he was appointed governor of the State of Queensland, the first time that a medical officer had been asked to fill such a distinguished political office During his five years at Brisbane he carried out his new duties with the energy, balance, and competence which he had shown in his medical administration At the end of his term of office he was appointed K C M G After his return to this country he was colonel commandant of the R.A M C from 1932 to 1938

He held many foreign awards and he was a commander of the Legion of Honour, the Belgian Order of Leopold, and the Crown of Italy He was an honorary fellow of the Royal College of Surgeons of Edinburgh, the Royal Australasian College of Surgeons, and the American College of Surgeons He was awarded honorary degrees by the Universities of Oxford and Michigan.

He married in 1897 Lilian Isabel Ronaldson, who survives him There were no children of the marriage

JAMES SINCLAIR BAXTER

M.A. Cantab, M.Sc, M.B Belf, M.D Brist, F R.C S I

Dr James Baxter, professor of anatomy in the University College of South Wales, died at his home in Cardiff on Sept. 11 at the age of 55

The son of a brilliant Irish lawyer, he studied at Belfast under the late Professor Walmsley, who early helped to direct his interest to embryology He graduated in science in 1926 and in medicine in 1929 He showed great academic ability and also took an active part in general student affairs, and was president of the Students' Representative Council After qualifying he spent some years in Belfast in house-appointments at the Royal Victoria Hospital and in a demonstratorship in the department of anatomy in Queen's University He took his F R.C.S.I and his M.SC in 1932 and for some time considered specialising in surgery But he finally turned to anatomy, and his embryological interests were further stimulated when he went to the Carnegie Institution in Washington with a Rockefeller fellowship in 1933 to work under Dr G L. Streeter

After serving as assistant professor of anatomy at McGill, and as a university demonstrator at Cambridge he was appointed to a readership at Bristol University He took his M D Brist. in 1946 with a thesis on the life history of the cells of the adrenal cortex. For many years he served as an active member of the medical board, and for three years as preclinical tutor In 1952 he was appointed to the chair of anatomy at Cardiff. He was a former vice-president of the Anatomical Society and had served on its council and on the editorial board of its journal. His own publications included *Aids to Embryology* and the revision of *Frazer's Manual of Embryology*

J M Y writes

"I first met Professor Baxter when he and I were young and raw members of the Anatomical Society, and had just decided that we would both like to make our careers in anatomy Our paths converged once again when I too came to Bristol in 1940 I shall always remember with gratitude his loyal and untiring service during the war years, when staffs were reduced to a minimum, the teaching load was heavy, and neither time nor facilities for research could be expected When war was over, he cooperated wholeheartedly in the development of our research programme, and we spent many an enjoyable hour working on the histochemistry of the suprarenal cortex under a variety of experimental conditions His scientific work reflected his character admirably, with its meticulous attention to even the smallest detail, and with scrupulous integrity in the presentation of his results "

Professor Baxter leaves a widow and a son, who is a doctor

HENRY ROBINSON

M A , M D Cantab , D L , J P

Dr Henry Robinson, who died on Sept 30 at the age of 83, practised for many years in Kensington But he was most widely known for his work for national professional organisations, including Epsom College, the Medical Defence Union, the Royal Medical Benevolent Fund, and the Medical Insurance Agency

He was educated at St Paul's School and at Trinity College, Cambridge His medical studies at St George's Hospital were interrupted by service in the South African war as a private soldier in the university contingent of the volunteer company of the 1st Battalion Suffolk Regiment He qualified in 1903 and, after house-appointments at St George's, Great Ormond Street, and the Royal Cancer Hospital, he set up in practice in Kensington in 1907 He also served as anæsthetist at the Royal Cancer and Samaritan Hospitals, and he edited the fifth edition of Hewitt's *Anæsthetics*

During the 1914–18 war he served in the R A M C From 1919 until 1937 he was a councillor and alderman of the Royal Borough of Kensington, and from 1928 to 1930 he was mayor From 1931 to 1937 he represented North Kensington on the London County Council He was also a justice of the peace and deputy lieutenant for London and served for ten years as an income-tax commissioner

In 1916 Dr Robinson was elected to the council of the Medical Defence Union and since 1928 he had been honorary treasurer From 1927 he was on the council of Epsom College, and he was chairman from 1936 to 1938 and honorary treasurer from 1952 until this year He worked tirelessly for the Foundation and collected over £9000 From 1938 he was on the management committee of the Royal Medical Benevolent Fund, and in 1955 he was appointed chairman of the case committee In 1938 he became honorary secretary of the Medical Insurance Agency, and in recognition of his services the Agency has endowed scholarships at Epsom College to which his name is attached

In 1911 he married Margaret, youngest daughter of the late Robert Barnes, F R C P , F R C S , the London obstetrician There are two sons and a daughter of the marriage

ERNEST WILLIAM GOODPASTURE

M D Johns Hopkins

Dr Ernest W Goodpasture, formerly professor of pathology at Vanderbilt University and dean of its medical school, died on Sept 20 at the age of 73 He is best known for his finding, in 1931–32, that fowl-pox and vaccinia viruses would grow on the chorio-allantoic membrane of the chick embryo This was the first demonstration that the chick embryo provided a good culture medium for viruses, and its use was developed extensively, particularly by Burnet and Cox and their colleagues A large number of virus vaccines used in medicine, both human and veterinary, thus stem from Goodpasture's discovery He himself was a self-effacing man who did little to publicise or capitalise this work

His many positions, besides his appointments at Vande University, included a Rockefeller fellowship in patholo Johns Hopkins, an assistant professorship at Harvard, the scientific directorship of the department of patholog the Army Medical Center in Washington. He also rece the research medal of the Southern Medical Association, Kober medal of the Association of American Physicians, the award of the American Association of Pathologists Bacteriologists

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The late Dr E K Macdonald qualified *from St Tho* Hospital, and not from *St* Bartholomew's Hospital as stated in obituary

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Diary of the Week

OCT 9 TO 15

Monday, 10th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Prof A C Dornhorst Asthma in Hospital
INSTITUTE OF EDUCATION, Malet Street, W C 1
5 15 P M Dr J M Tanner Physical Development. (First of
lectures)

Tuesday, 11th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 30 P M *Experimental Medicine and Therapeutics* Dr L G Lajtha
Dr P Mary Cotes Kinetics and Control of Erythropoiesis
8 P.M *Psychiatry* Dr Noel Harris Prevention of Mental Stress
Disorder (Presidential address)
ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M (Wright-Fleming Institute) Mr Stanley Way Carcinoma of
Vulva
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr I A Magnus Effects of Physical Agents
ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P M Prof Charles Wells Urethral Injuries and the Treatmen
Stricture
BIRMINGHAM MEDICAL INSTITUTE, 36, Harborne Road, Birmingham
8 P M *Psychiatry* Dr F J Fish Existentialism and Psychiatry
MANCHESTER MEDICAL SOCIETY
8 P.M (Medical School, University of Manchester) *Surgery* Mr H
Simmons On Ulcerative Colitis *(Presidential address)*
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P.M (General Infirmary at Leeds) Dr Roger Gilliat New Stu
of Peripheral Nerve Conduction

Wednesday, 12th

POSTGRADUATE MEDICAL SCHOOL
2 P M Prof G H Lathe Biochemical Basis of Liver Function Tests.
ROYAL SOCIETY OF MEDICINE
4 30 P M *Physical Medicine* Dr P H Sandifer, Mr G Lloyd Robe
Dr K Nicholls Palmer Treatment of Cerebral Palsy
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Yvonne Clayton Fungi Causing Human Disease
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr R W Riddell Diagnosis of the Pulmonary Mycoses.
INSTITUTE OF NEUROLOGY, Queen Square, W C 1
5 30 P M Sir Russell Brain Cerebral Basis of Mind
MANCHESTER MEDICAL SOCIETY
5 P M (Medical School, University of Manchester) *Pathology* Dr J
Emery Sudden Death in Infancy
UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Mr J B Farquhar Infertility
6 P M Mr T F Redman Pre-eclampsia

Thursday, 13th

UNIVERSITY OF LONDON
5 P M (Royal Veterinary College, Royal College Street, N W 1) Pr
C W Emmens (Sydney) Biological Assay of Œstrogenic and An
œstrogenic Activity
INSTITUTE OF DERMATOLOGY
5 30 P M Dr J S Pegum Pilo-sebaceous Units, Hair Cycle, Anoma
of Hair Growth
ALFRED ADLER MEDICAL SOCIETY
8 P M (11, Chandos Street, W 1) Modern Trends in Indivi
Psychology

Friday, 14th

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr Charles Drew Aspects of Profound Hypothermia in Car
Surgery
4 P M. Prof R R H Lovell (Melbourne) Coronary and Hypertensi
Problems
KING'S COLLEGE HOSPITAL MEDICAL SCHOOL, Denmark Hill, S E 5
1.30 P.M Sir James Paterson Ross Principles of Surgery (Thom
Percy Legg lecture)
PLYMOUTH MEDICAL SOCIETY
8.30 P.M (North Friary House) Dr J W Landells Dangers of Med
Treatment.

Saturday, 15th

FACULTY OF RADIOLOGISTS
9 30 A M (Royal Infirmary, Cardiff) Provincial meeting.
BRITISH ASSOCIATIO OF SPORT AND MEDICINE
10 A.M (Arthur Stanley Institute, Peto Place, Marylebone Road, N W 1
All-day meeting

Notes and News

THE CONGO

Dr J. S. McKenzie Pollock, senior W.H.O. representative in the Congo, says that the effects of the discontinuation of preventive measures are now being seen. In one recent week, four separate outbreaks of smallpox were reported, and the public-health services are not in a position to combat this serious epidemiological threat. Stocks of vaccine are available thanks to the Nigerian Government, but a large vaccination programme cannot be started until technical staff from outside can be provided to give leadership to the local teams. While the smallpox situation gives dramatic indication of the breakdown in the health services, other disease patterns are also showing significant deterioration. In the Bunia area, for instance, an outbreak of bubonic plague is being investigated, disquieting reports are being received of an increase of malaria and filariasis, while, if preventive measures are not restarted, an increase in the incidence of sleeping-sickness can also be expected.

The W.H.O. advisory team has drawn up a list of doctors and senior technicians needed to reactivate the public-health services. About 100 qualified staff are needed to cope with the epidemiological situation, and another 300–400 before the end of the year. When this total is reached, not only the preventive health services but also the medical-care services can become fully operative—even after the Red Cross and Red Crescent, as well as Government, medical teams have been withdrawn. The services of most of these were made available for three months only, and the U.S.S.R. team (20 doctors and 4 interpreters) as well as the Israeli team (8 doctors and 5 nurses and technicians) have now been withdrawn. As an interim measure, five further Red Cross teams are being called upon.

The medical personnel will be under contract to the Congolese Government, but they will have the protection of the United Nations, as well as a salary guarantee.

WORLD FOOD PRODUCTION

ESTIMATES by the Food and Agricultural Organisation for world agriculture production (excluding China) show a rise of about 2% in 1959–60, compared with 5% in each of the two preceding seasons. In its annual study, *The State of Food and Agriculture*[1], F.A.O. says that the increase "is a little less than the average for recent years, but it slightly exceeds the estimated annual population growth of 1.6 per cent." Much of it was in the Far East, where (excluding China) agricultural production per person is now only 3% below the level before the second world war. But Mr B. R. Sen, the director-general, says in his foreword that much greater increases are needed in these regions "before any real progress can be made in stamping out hunger and malnutrition." In the less developed regions, the increased production so far "has come primarily from an enlargement of the cultivated area, and for most products the potential contribution from higher yields and productivity has as yet scarcely been tapped." On the whole the gap between food-supplies in the more-developed and less-developed regions has tended to widen rather than narrow in recent years. Stocks of grain in the exporting countries have reached an unprecedented level.

STOPPING SMOKING

MANY smokers would like to abandon the tobacco habit but fail when they try. For this reason advice on the subject is always welcome.

As an experiment for a year, a "tobacco weaning clinic" was established in Copenhagen, and Dr Rosenberg, the director, has published his methods and results both at this clinic and in private practice.[2] [3] The remedies used were (*a*) tablets containing 2.5 mg. silver acetate to make the smoke taste nasty, (*b*) a tranquilliser to reduce unrest, (*c*) psychotherapy, both to allow the smoker to talk about his problems and to strengthen his motives, (*d*) relaxation therapy, and (*e*) the keeping of a daily record of self-examination. Group therapy seemed to have advantages, and where husband and wife took the cure together the results were better than when they did so separately. Rosenberg reports that nearly half (40%) of the patients were abstainers at the end of six months. Most of those who lapsed smoked less than they had done.

Rosenberg thinks that patients who want to stop smoking need help, but treatment can seldom be given effectively by the general practitioner. It requires the coordination and teamwork of a clinic, and he concludes that "a tobacco weaning clinic under the leadership of the public authorities should be a place where people suffering from the smoking habit can seek help and assistance."

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[1] Obtainable from H.M. Stationery Office at 10s.

[2] Rosenberg, A. *Ugeskr. f. Læg.* May 28, 1959.

[3] Rosenberg, A. *ibid.* May 26, 1960.

University of London

Dr P. E. Polani has been appointed to the new chair of pædiatric research at Guy's Hospital Medical School. The chair has been endowed by the National Spastics Society, and is to be named after Prince Philip, who is the society's president.

Dr Polani was born in Trieste in 1914 and graduated in medicine at the University of Pisa in 1938. He came to Britain for postgraduate study and took the D.C.H. in 1945. In 1948 he was awarded a National Birthday Trust Fund fellowship in the department of child health at Guy's, and the same year he took the M.R.C.P. In 1950 he became assistant to the director of the department. In 1955 he was appointed research physician on cerebral palsy to the National Spastics Society, and three years later he became director of the society's medical research unit in the department of child health at Guy's. He has published experimental work on the distribution of cholinesterases, the behaviour of nerve-fibres in fluorescent light, and the neurological disorders and congenital anomalies of children.

The title of reader in hæmatology has been conferred on Dr Sidney Shaw, and of reader in bacteriology on Dr H. I. Winner, in respect of their posts at Charing Cross Hospital Medical School.

Prof. Jean Piaget, who holds the chair of experimental psychology in the University of Geneva, is to give a lecture at 5.15 P.M. on Monday, Oct. 17, at the Senate House, Malet Street, W.C.1. His subject will be the Thinking of Young Children.

University of Leeds

At a recent examination for the degree of PH.D. (in medicine) J. W. Czerkawski was successful.

Royal College of Physicians of London

On Thursday, Nov. 3, Dr W. I. Card will give the Bradshaw lecture. He will speak on the Concept of Gastric Secretory Cell Mass. On Thursday, Nov. 17, Prof. D. V. Hubble will give the Langdon-Brown lecture. His subject will be the Endocrine Orchestra. On Tuesday, Nov. 29, and Thursday, Dec. 1, Dr K. D. Keele is to give the FitzPatrick lectures. His subject will be Evolution of Clinical Methods in Medicine. All lectures will be given at 5 P.M. at the college, Pall Mall East, S.W.1.

Society of Apothecaries of London

At the inaugural meeting of the first British Congress on the History of Medicine and Pharmacy, held in Apothecaries' Hall, London, on Sept. 29 the honorary fellowship of the Faculty of the History of Medicine of the Worshipful Society of Apothecaries of London was conferred, in absentia, on Sir Geoffrey Keynes, consulting surgeon to St. Bartholomew's Hospital, and Prof. Owsei Temkin, director of the institute of the history of medicine in Johns Hopkins University, Baltimore. These are the first awards of their kind.

The annual master's day service will be held at the church of St. Mary, Aldermary, on Sunday, Oct. 23, at 11.15 A.M.

Abortion Law Reform Association

The annual general meeting will be held on Tuesday, Oct. 25 at 6.30 P.M. in the Conway Hall, Red Lion Square, London, W.C.1. A public meeting will follow at 7.15 P.M., when Dr Glanville Williams will preside and Dr G. I. M. Swyer will speak on Oral Contraception.

College of General Practitioners

Today, Saturday, Oct 8, at 2 15 P M, at the Royal Free Hospital, Gray's Inn Road, London, W C 1, Prof Sheila Sherlock will discuss the differential diagnosis of jaundice

Scottish Conjoint Board

The following have been granted the licence of the Royal Colleges of Physicians and Surgeons of Edinburgh, and the Royal Faculty of Physicians and Surgeons of Glasgow

Eufrasio Bengoechea Gonzalez, J O Djan, H H Grosser, Mohamed Nawaz Kaleel, Jolaolu Olusegun Mojola, T S Twyble

National Marriage Guidance Council

On Oct 4 Mr R A Butler, the Home Secretary, opened the Council's new headquarters at 58, Queen Anne Street, London, W 1

International Federation of Surgical Colleges

This Federation is to hold a meeting from Oct 18 to 20 in London at the Royal College of Surgeons of England The theme of the meeting will be the Training of Surgeons, and the speakers will include Prof Digby Chamberlain and Mr Harold Edwards On Thursday, the 20th, at 5 P M Prof J F Nuboer, of Holland, will give a Moynihan lecture Further particulars may be had from the secretary of the Federation, Royal College of Surgeons of England, Lincoln's Inn Fields, W C 2

Medical Insurance Agency

At the annual meeting on Sept 15, Dr James Fenton, who has been chairman for 13 years, and Sir Henry Souttar, who has served for over 33 years, retired from the committee of management Mr R W Raven was elected chairman, and Prof Thomas Anderson, Sir John Richardson, and Dr D P Stevenson were elected to the committee Business in all departments reached new high levels during 1959 and the medical charities will benefit by over £38,000 by allocations from the year's surplus

Society of Chiropodists

The annual convention was held from Sept 15 to 17 at Norwich

Surgery sessions were held at the Norfolk and Norwich Hospital and the West Norwich Hospital by Mr R B Birt, Mr G K McKee, Mr L M Rouillard, Mr J P Stephens, Mr J C Taylor, and Mr N J Townley Lectures were given by Mr McKee on artificial joints of the lower limb, Mr Rouillard on pedicle grafts, and Dr A J Rook on the mind and the skin Dr H L Collins gave an account of chiropody as practised in the United States, and Mr H Rosenstein, chief chiropodist of the London County Council, lectured on the chiropodial management of the pre-gangrenous foot

Middlesex Hospital Medical School

At the annual dinner in London, on Sept 30, Mr J P Monkhouse, the chairman, reviewed the highlights of the past year

The system of exchanging staff with the University of Toronto was working admirably, and Sir Eric Riches is at present in Canada The first part of the new medical school, "for so long a dream", had been opened last December by Lord Astor of Hever, whose generosity had made this project possible The children's ward was now extended and modernised, and a much-needed additional operating-theatre had been built, but the diet kitchen had been modernised only by means of a grant from the hospital endowment fund

Prof B W Windeyer, dean of the medical school, spoke in particular of academic achievements and changes

Biology as applied to medicine is to be taught to future preclinical and clinical students, and a new chair has been established in this subject, with the help of the Nuffield Foundation The University of London has agreed to the establishment of a department of psychiatry, and plans are in hand for developing a department of nuclear medicine and for a chair of obstetrics when possible A donation has also been made by the Wellcome Trust for the construction of new pharmacological research laboratories

Dr J D Hamilton, the senior Broderip Scholar, spoke mostly of the school's less academic activities—the successes in drama and in sport, including the Olympic Games, and the expedition to the Himalayas to study physiological and psychological function In conclusion Mr A J B Goldsmith proposed The Chairman

Sir James Paterson Ross has succeeded Sir Francis Fraser as chairman of the civil consulting staff of the King Edward VII Convalescent Home for Officers at Osborne, Isle of Wight Dr R M Mason has been appointed an honorary member of the consulting staff

Mr A V S de Reuck, formerly assistant editor of *Nature*, has been appointed deputy director of the Ciba Foundation for the Promotion of International Cooperation in Medical and Chemical Research, London Miss M P Cameron has returned to the Ciba Foundation as scientific assistant and librarian after five years in the United States

Mr E A Nicoll is visiting Greece and Israel on behalf of the British Council

The Medical Research Council asks that in future all requests for compounds in the Steroid Reference Collection should be addressed to Prof W Klyne, Chemistry Department, Westfield College, Hampstead, London, N W 3, and not to the Postgraduate Medical School at Hammersmith

A meeting of the Listerian Society is to be held on Tuesday, Oct 11, at 8 30 P M, at King's College Hospital Medical School, Denmark Hill, London, S E 5, when Dr Richard Asher will speak on Medical Salesmanship

The Society of Cardiological Technicians of Great Britain is to hold an exhibition of cardiological apparatus at the Londoner Hotel, Welbeck Street, London, W 1, on Oct 14 (5 30 P M to 8 P M) and 15 (9 30 A M to 1 P M)

The St Thomas's Hospital old students' dinner will take place at the Savoy Hotel, London, W C 2, on Friday, Nov 11, at 7 30 P M Tickets (£2 5*s*) may be had from hon secretaries at the hospital

The address of the International Hospital Federation is now 24, London Bridge Street, London, S E 1

CORRIGENDUM *Incidence of Surgical Wound Infection in England and Wales*—In this report of the Public Health Laboratory Service (Sept 24, p 659) the last column of table I should have been headed "No pathogens isolated"

Appointments

BURRELL, P S R, M B Leeds, D P H M O H Redcar, Saltburn, and Marske by-the Sea

CALEY, J P, M B Sheff, M R C P part time consultant physician, Mansfield area

COWHEY, Ellen M, M B Dubl, D P H assistant M O H and school M O, Leicester

GIFFIN, W D, M B Edin, F R C S E, M R C O G consultant obstetrician and gynæcologist, Dundee and Angus area based on Dundee teaching hospitals

MCCORMACK, JOHN, M B Durh, D P H area executive M O for the North no 1 and 2 areas and M O H, Berwick, Alnwick and Amble, Belford, Glendale, Norham and Islandshires, and Rothbury

MATTHEWS, R A, M B Lond assistant M O and school M O, southern part of Buckinghamshire

MOFFITT, LEDA P, L M C C, D I H deputy M O H, Slough, and assistant county M O and school M O, Buckinghamshire

WITHNELL, ALLAN, M D, B SC Manc, D I H M O H Morley and Ossett, Horbury, and Wakefield

Lancashire County Council

BARNETT, MARION B, M B Durh assistant divisional M O, Bury area
BERGIN, M B, M B N U I assistant divisional M O, Winwick area
BILBER, S M, M R C S, D T M & H, D P H, D I H assistant divisional M O, Accrington area
BISHOP, MARGARET, M B Lond assistant divisional M O, Farnworth
BLOCKEY, PAULINE, M B Manc, D I H assistant divisional M O, Ashton under-Lyne area
CARDWELL, MARY R, L R C P I assistant divisional M O, Standish area
FALCONER, W R, M B Glasg, D P H assistant divisional M O, Morecambe
GAYE, WILHELMINA N, M R C S, D I H assistant divisional M O, Fylde
HALL, CATHERINE E, M B Manc, D OBST, D C H assistant divisional M O, Atherton
JONES, BRENDA, M B Lpool, D I H assistant divisional M O, Liverpool area
LINNELL, PATRICIA E, M B Lond assistant divisional M O, Leigh area
MARSHALL, D C, M B Glasg assistant divisional M O, Fylde
MILLION, RAYMOND, M B Manc assistant divisional M O, Royton Crompton
O'GORMAN, JOSEPH, M B N U I, D I H assistant divisional M O, Ormskirk area
O'NEILL D W J, M B assistant divisional M O, Preston area
SMITH, FREDERICK, M B Manc, D C H assistant divisional M O, Lancs
TALBOT, J C, M R C S assistant divisional M O, Leigh
WHITTAKER, G R, M B Manc assistant divisional M O Colne area
YULE, I G, M B Manc assistant divisional M O, Middleton

The Lancet · Saturday 15 October 1960

THE SIGNIFICANCE AND CLASSIFICATION OF FAT-EMBOLISM

SIMON SEVITT
M.D, M.Sc. Dubl., F.R.C.P.I, D.P.H
CONSULTANT PATHOLOGIST, BIRMINGHAM ACCIDENT HOSPITAL AND MEDICAL RESEARCH COUNCIL BURNS AND INDUSTRIAL INJURIES RESEARCH UNIT, BIRMINGHAM, 15

ALTHOUGH pulmonary fat-embolism is very common after injury, its clinical significance has been greatly overestimated On the other hand systemic embolism is less frequent but more likely to be significant, mainly because of cerebral involvement Nevertheless, fat-embolism continues to be classified clinically into pulmonary and cerebral forms, suggesting that pulmonary emboli produce symptoms, and often a cardiac form is added This confusion has arisen (1) because cardiovascular effects of hæmorrhage and oligæmia have often been attributed to fat-embolism, (2) because non-embolic pulmonary complications have been considered to be of embolic origin, and (3) because the respiratory symptoms and tachycardia, which are often part of unequivocal clinical embolism, have little to do with emboli in the lungs Myocardial embolism is being studied, but provisional results show that it, and its possible effects, are overestimated

The present analysis is based on data of three kinds—a clinicopathological study of 100 injured cases reaching necropsy, a later group of special cases which also died, and a study of 20 patients with clinically diagnosed systemic embolism The picture and severity of systemic embolism varies widely from rapidly fatal fulminating forms, diagnosed only at necropsy, to mild, almost subclinical, effects Failure to appreciate this is partly responsible for difficulties in diagnosis, and for the widely divergent views as to prognosis

Pulmonary Fat-embolism

Heavy pulmonary embolism is closely related to the severity of injury, and in particular to the multiplicity of fractures and the speed of dying (Sevitt 1957, Emson 1958), but pathological, clinical, and experimental evidence now indicates that even histologically gross embolism (naturally occurring) is unlikely to be important

The pulmonary congestion, œdema, small hæmorrhages, and foci of collapse, which are said to result from capillary blockage and endothelial anoxia, are mainly due to non-embolic causes, thoracic, abdominal, and cerebral trauma all tend to produce pulmonary congestion and œdema, whilst terminal and agonal effects are often difficult to eliminate The weight of the lungs and the histological degree of embolism do not correlate (Scully 1956), whilst the fluid nature of the embolic fat at body temperature raises doubts as to whether the alveolar capillaries are completely blocked (Wilson 1946)

In previously healthy patients dying during the first few days after injury respiratory distress is not common, even though pulmonary embolism may be considerable—provided that cerebral and thoracic injuries are absent, that blood-loss has been corrected by transfusion, and that cerebral fat-embolism is not present Further, many cases of clinical systemic embolism do not have respiratory symptoms, and yet systemic embolism is nearly always associated with a heavy degree of pulmonary fat-embolism at necropsy (Sevitt 1957, Emson 1958)

Experimentally the intravenous injection of fat can produce acute respiratory distress, venous congestion, and even death, but, as Scriba (1880) and Cohnheim (1889) first pointed out, the lungs then show a very heavy degree of embolism which is never seen in man The dose needed to produce these effects is high (Lehman and Moore 1927, Harris et al. 1939, Scuderi 1941), and Armin and Grant (1951) showed that the fat extractable from the lungs of patients dying with gross embolism is only a fraction of what would be required.

Serious effects were produced if shock or blood-loss was also present (Gold and Loeffler 1923, Green and Stoner 1950, Harman and Ragaz 1950, Whiteley 1954), but again the amount of fat injected was much greater than that necessary to produce embolism comparable to gross embolism in man. Armin and Grant (1951) showed that, when this dose was given to rabbits which were also subjected to considerable hæmorrhage, it did not add to the illness or the mortality, nor did the injection of fat into bled animals hinder the beneficial response to blood-transfusion

It seems reasonable to conclude that pulmonary fat-embolism does not cause significant symptoms or produce serious lung changes in previously healthy subjects, and that it is not responsible for death even in patients with shock or hæmorrhage The lack of effect is presumably related to the large functional reserves and enormous capillary bed within the lungs, and to the fluid nature of the emboli

Systemic Fat-embolism

A full analysis of systemic embolism must include cases which were found at necropsy but unsuspected during life, and those which were diagnosed clinically, some of whom die and reach necropsy (see Sevitt 1959)

At necropsy, systemic embolism (based on fat-emboli in vessels of the brain or in glomeruli, or both) is less common than the pulmonary form with which it is always associated

In a series of 100 necropsies at the Birmingham Accident Hospital, none of whom were suspected of having clinical embolism, 24% had systemic embolism and 89% had pulmonary embolism, and all those with systemic emboli had pulmonary emboli (Sevitt 1957, 1959, Emson 1958) Systemic embolism was found in 59% of the 32 patients with numerous pulmonary emboli, but in only 9% of the 57 patients with few or moderate numbers of emboli in the lungs Systemic embolism had occurred in 45% of those with severe bony injuries, but in only 7% of those with mild or moderate bony injuries In a third of the cases systemic embolism was relatively heavy, and all those patients had gross pulmonary embolism and multiple fractures

Analysis of the case-records showed that cases with systemic embolism at necropsy could be divided into those which had had unexplained cerebral and other symptoms consistent with fat embolism (7 cases), and those without significant symptoms (17 cases) In 4 cases cerebral embolism was considered to be the main cause of death, symptoms regarded as significant were unexplained drowsiness, coma or failure to recover consciousness after anæsthesia, and unexplained cerebral irritation such as convulsions, athetoid movements, and epilepsy when there was no evidence of cerebral injury The number of such cases was probably underestimated because cerebral embolism was possibly significant in some of those with traumatic cerebral contusion Other workers have made similar correlations Grant and Reeve (1951) found histological systemic embolism in 13 cases dying after limb injury, 5 of which had relevant cerebral effects, whilst Scully (1956) concluded that in only 1 of his 19 cases was systemic embolism the cause of death.

I have kept in mind the clinical difficulty in diagnosing cerebral embolism in assessing the symptoms and cause of death of patients with fractures At necropsy the brain is carefully examined for petechiæ in the white matter, and rapid frozen sections of brain and kidney for lipid are now often made, by this means 8 other cases of unsuspected cerebral fat-embolism causing or contributing to death have been revealed in this hospital during the past year It is clear that some of the unsuspected cases with histological systemic (and cerebral) embolism are clinically important and may be fulminating cases (see later), whilst others seem to be subclinical

Systemic embolism varies considerably in its severity and clinical picture, and may be classified into (1) fulminating cases, (2) the classical or full syndrome, and (3) a number of incomplete or partial syndromes

Fulminating Cases

The injuries are generally severe and multiple fractures are usually present, these patients die one to three days after injury, even though hæmorrhage and oligæmia may have been adequately combated by early and efficient transfusion As noted above, these cases are usually recognised by retrospective correlation of unexplained cerebral symptoms with cerebral fat-emboli at necropsy

A common story is that the patient was initially conscious after injury but became stuporose and then comatose, sometimes within a few hours and generally within one or two days The onset of coma may be masked by general anæsthesia for surgery, but consciousness does not return There may be weakness of one or more limbs or occasionally hemiparesis Epileptiform or choreoathetoid movements—focal, unilateral, or generalised—may occur Collapse during resuscitation or failure to maintain benefit after blood-transfusion may dominate the picture, hence fulminating cerebral embolism may be one of the causes of “ irreversible shock ” (Sevitt 1958)

Rapid onset of serious symptoms may also occur in patients with single fractures

Example—A man of 25 was admitted with a compound fracture of the leg His general condition was satisfactory, and he was conscious Sixteen hours later he had a headache, and he vomited and became drowsy Weakness of the right arm and leg was noted Extradural hæmorrhage was suspected and burr holes were made in the skull, but no hæmorrhage was seen He remained unconscious and died thirty-two hours after injury Necropsy showed petechiæ in the cerebral and pontine white matter, and in parts of the cortex, and frozen sections of the brain, kidney, and other organs revealed fat-emboli

Fulminating fat-embolism is of course difficult to diagnose Clinically death may be attributed to the delayed effect of a head injury (there is added difficulty if the patient was concussed), to an anæsthetic misadventure, or to other causes of post-traumatic coma A petechial eruption is absent or very sparse, and easily overlooked presumably because the patient dies before it normally appears Even a few characteristically located skin petechiæ may be of great help in differential diagnosis, renal biopsy for glomerular embolism can also be helpful (see below)

At necropsy the petechial hæmorrhages in the white matter of the cerebrum may be few or ill defined if death has occurred within a day or so of injury, often the white matter only shows a somewhat excessive vascular punctation without definite hæmorrhagic spots Frozen sections of the brain stained for lipid are essential for diagnosis, and should form a routine part of the histology of all subjects with fractures reaching necropsy

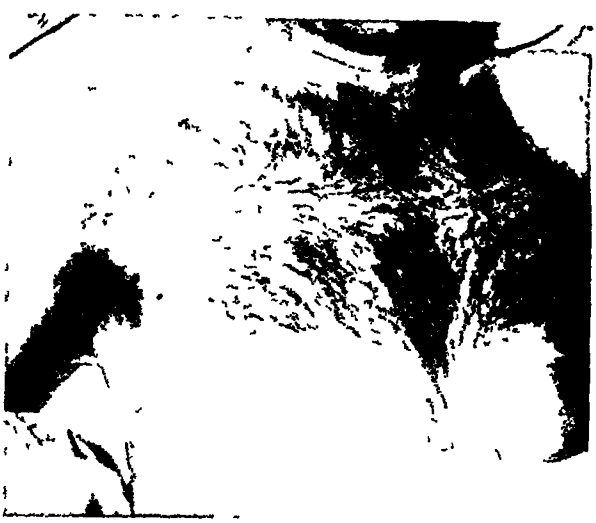

Fig 1—The petechial rash of fat-embolism characteristically located in front of the upper part of the chest and shoulders

The Classical Syndrome

This well-known picture is characterised by major cerebral and neurological effects, respiratory symptoms, pyrexia, tachycardia, and a characteristic petechial eruption of much diagnostic importance (fig 1)

The first symptoms generally develop within twenty-four hours of the accident, and not about the third day, as is commonly stated In the records of 75 cases, some published and others personally observed, symptoms were present in 23% within twelve hours of injury, in 60% within twenty-four hours, in 80% within thirty-six hours, and in over 90% within forty-eight hours The early symptoms are important because their significance may be overshadowed by other effects of injury, recognition is often delayed until the disorder of consciousness is serious, or the rash attracts the clinician's attention

The *onset* is often sudden A pyrexia of 102–103° F or even higher, and a tachycardia of 100–120 per minute are usual Cerebral and respiratory symptoms develop simultaneously or at different times, and one or other may predominate Restlessness, delirium, and insomnia often precede or accompany mental confusion or stupor which may later deepen into coma Other possible neurological symptoms include incontinence, convulsions, disturbances or pupillary reflexes, spasticity, increase or loss of deep reflexes, and even paralysis of a limb or muscle-groups

Respiratory distress is manifest by dyspnœa, polypnœa, possibly cyanosis, and tightness in the chest Moist sounds in the lungs, cough, and sputum may be present The respiratory effects cannot be due to the pulmonary emboli (see below), and they are presumably neurogenic in origin from cerebral emboli Neurogenic pulmonary œdema is now well recognised, whilst acute respiratory symptoms not uncommonly complicate acute cerebral disease, such as spontaneous and traumatic cerebral hæmorrhage, and brain operations (see Cameron 1948) Thus respiratory effects from cerebral emboli are not surprising

The *blood-pressure* does not fall unless oligæmia was untreated or until terminal cardiac failure supervenes Thus the so-called “ cardiac syndrome ” is a myth, and was probably due to the accompanying effects of untreated hæmorrhage. The jugular veins are rarely distended even when blood-transfusion is in progress

The *petechial eruption* is preceded by other symptoms, and it usually develops on the second or third day after injury (fig 1) It appears on the front of the shoulders, the root of the neck, and the upper parts of the chest, it may be restricted or extend over the arms, upper abdomen, and even the thighs The petechiæ are often fine red spots, though sometimes they are relatively coarse They appear in crops over a day or two, each crop fading within a few days The uninitiated may mistake the combination of pyrexia and a petechial eruption for septicæmia.

The mortality in this type is likely to be high because of the coma, but it can be reduced by modern treatment for comatose patients In recent years heparin therapy has had its advocates, but its effectiveness remains unproved There was 1 death among the 4 classically complete cases which I investigated.

Incomplete and Partial Syndromes

In most clinically diagnosable cases some of the classical symptoms are absent. The course is usually less severe than in the classical picture, and many cases are mild 16 of the 20 cases of systemic embolism which I studied showed an incomplete or partial clinical picture, all survived Primary diagnosis was made from the characteristic petechial rash, affected skin from the shoulder was biopsied in 10 cases, and the diagnosis was confirmed by finding embolic fat globules in dermal capillaries (fig 2)

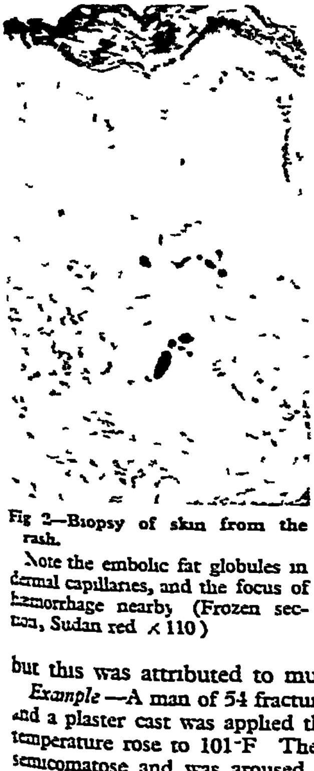

Fig 2—Biopsy of skin from the rash.

Note the embolic fat globules in dermal capillaries, and the focus of hæmorrhage nearby (Frozen section, Sudan red ×110)

These cases subdivide into 3 groups

Those without respiratory symptoms, but with cerebral and sometimes neurological symptoms, pyrexia, tachycardia, and a petechial rash (5 cases)

The cerebral effects were severe in 1 patient (stupor, semicoma, incontinence, and temporary paresis of one arm), but in the others they were relatively mild (mental confusion in all 4 and retrograde amnesia in 1) The patient with amnesia also had respiratory difficulty, but this was attributed to multiple rib fractures

Example—A man of 54 fractured his right tibia and fibula, and a plaster cast was applied the same day Next day, his temperature rose to 101°F The following night he became semicomatose and was aroused with difficulty, temperature 102 F, pulse 96 per min He became incontinent of urine and his right arm was noticeably weaker than the left A stroke was suspected, but by the third day a petechial rash appeared on his shoulders and later spread to the chest. A skin biopsy specimen revealed fat emboli in the dermal capillaries The patient remained stuporose for a few days, with some spasticity of the limbs, but by the eleventh day after injury he had recovered except for occasional incontinence. Respiratory effects were conspicuously absent.

Those without cerebral symptoms, but with respiratory distress or polypnœa as well as pyrexia, tachycardia, and a petechial rash (4 cases)

Example—A man aged 41 was run into by a car and knocked out for a few seconds His knee was swollen from a fissure fracture of the upper end of the tibia involving the joint, the leg was splinted Next evening his temperature rose to 103 F, pulse-rate 120 per min., and he complained of headache. There was slight dyspnœa. A petechial rash in front of the chest and shoulders established the diagnosis, which was confirmed by skin biopsy and by the finding of fat globules in the urine Next day he became very dyspnœic (respiratory-rate 60–70 per min), and an oxygen tent was necessary Radiographs showed a diffuse patchy shadowing of both lung fields His temperature was now 104°F, and the rash had spread to the front of the abdomen and thighs He was mentally clear, there were no cerebral symptoms or neurological signs, and he was not incontinent

Those without significant cerebral or respiratory symptoms (7 cases) Diagnosis was based on the characteristic petechial rash, in 2 cases skin biopsy was done and confirmed the diagnosis Pyrexia and tachycardia were variable

Example—A man of 20 sustained a compound comminuted fracture of the tibia This was plated next day under general anæsthesia, and he was transfused with 4 bottles of blood. The following day his temperature was 100–101°F, and a petechial rash appeared over the front of the chest and arms He was otherwise well except for some lower abdominal pain, there was no cough, dyspnœa, or mental symptoms Fat-embolism would never have been considered but for the rash.

Systemic Embolism Without Petechial Rash

Without the rash the possibility of fat-embolism is rarely suspected or is on much less certain ground Some patients die from embolism or from other causes, and, no doubt, many survive Several cases other than the fulminating ones, with cerebral fat-embolism at necropsy, had obscure cerebral symptoms during life but had no rash, whilst others were without significant cerebral or respiratory symptoms No doubt many survive with or without cerebral effects of embolism, and in some the only symptoms are pyrexia or tachycardia

Aids to diagnosis would be most helpful in the severe cases without a rash Unfortunately no reliable simple test has been developed, and diagnosis still largely depends on clinical acumen The finding of fat in the sputum is common, but at most indicates pulmonary embolism Examination of the urine for fat is unreliable Several samples of urine were examined from most of the present cases but in only 2 was fat detected. This contrasts with the report of Musselman et al. (1952), who found urinary

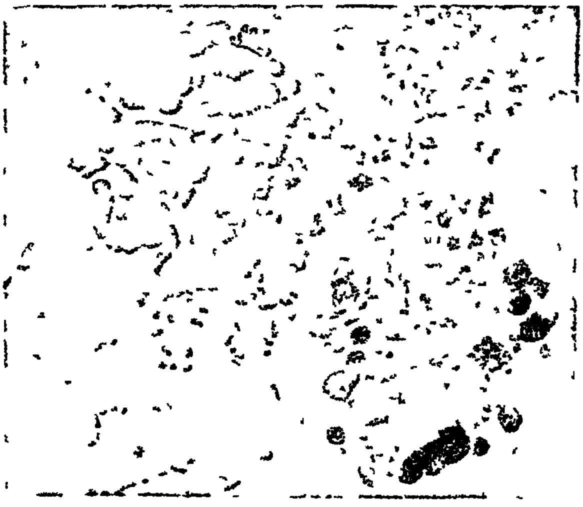

Fig 3—A heavy degree of glomerular fat-embolism. (Frozen section, Sudan red ×105)

fat in over 50% of 109 injured patients (and in 12% of 50 uninjured patients), but they examined 15 consecutive twenty-four-hour specimens of urine from each patient. Of course negative results may be due to incomplete emptying of the bladder since fat floats in urine. Microscopy of the plasma for globules of fat has been described (Peltier 1954, 1956) but the test is still in the experimental stage, and further work is needed to relate the pathological and clinical evidence of embolism.

Renal Biopsy

Needle biopsy of the kidney, which can be of value, should be considered in special cases—e.g., obscure post-traumatic coma. I have used it when craniotomy was being considered for possible intracranial hæmorrhage. The finding of glomerular fat-emboli is proof of systemic embolism (fig. 3) and, by inference, cerebral embolism. Using the Vim-Silverman needle the biopsy is not difficult and is relatively safe. Rapid frozen sections should be stained for lipid, or, if this cannot be done quickly, part of the thin core of the renal tissue obtained should be flattened between glass slides, and then stained for fat with a fat-soluble dye. Unequivocal fat-emboli in glomerular capillaries are easy to recognise under the microscope.

Discussion

Although pulmonary fat-embolism is very common after injury and almost universal after fracture of marrow bones, evidence from clinical, pathological, and experimental sources strongly indicates that it rarely, if ever, causes significant symptoms or produces pathological changes in the lungs. This presumably reflects the large reserves of the lungs and the fluid nature of the emboli. Trapping of the emboli may be considered physiological rather than pathological, and it is also protective in that fewer or no emboli will then reach the systemic circulation. On the other hand, systemic embolism can be clinically important, but only a fraction of those with pulmonary emboli at necropsy have systemic emboli. The frequency of systemic embolism at necropsy is higher when pulmonary embolism is relatively gross, and when many marrow bones are fractured. This is in apparent contradiction to ordinary clinical experience, because most cases of systemic embolism are diagnosed in patients with a fracture of one or at most two long bones, usually the tibia or femur. But the discrepancy is more apparent than real, because a necropsy series will naturally include many severely injured patients with multiple fractures (in whom the likelihood of systemic embolism is high), whilst the clinically diagnosed cases are found among a much larger group of injured survivors, most of whom have less severe injuries and fewer fractures.

The prognosis of clinical embolism is particularly affected by the presence and severity of cerebral symptoms. The mortality of those in coma is relatively high, whereas it is low in those with mild cerebral effects or without cerebral symptoms. The greater frequency of cases of mild or moderate severity, of which a variable proportion go undiagnosed, is responsible for the variable reports of prognosis. This point is important if potential remedies are to be properly assessed, the mild and less severe cases will recover with or without treatment, but the group of comatose patients has a relatively high mortality.

Necropsy evidence also indicates that mild and even subclinical cases of systemic embolism are not infrequent. Some of the cases discovered at necropsy had apparently never developed symptoms referable to the emboli, and had died of other causes. Thus some patients seem to tolerate some embolic fat in the brain, whilst in others various degrees of cerebral disorder are produced. Histologically, scantiness of cerebral emboli is related to absence of cerebral effects, but at necropsy, in a series of which none was clinically suspected of embolism, it can be difficult to pick out histologically the symptom-producing from the subclinical emboli.

Summary

An analysis of the significance and classification of fat embolism is based on material from 100 cases dying after injury, and from 17 clinically diagnosed patients.

Histological evidence shows that pulmonary fat-embolism is very common after injury but rarely causes symptoms or produces abnormal changes in the lungs. Systemic (including cerebral) embolism varies considerably in its severity and symptoms. Prognosis mainly depends on the presence of coma.

Systemic embolism is divisible into (1) fulminating cases, dying in coma within a day or two of injury, (2) the classical syndrome of cerebral and neurological symptoms, with respiratory distress, pyrexia, tachycardia, and a characteristic petechial rash, and carrying a high mortality, and (3) incomplete and partial syndromes, in which cerebral or respiratory effects, or both, are absent, and in which mortality is low.

The rash is of importance in diagnosis, and cases without a rash are difficult to diagnose. Needle biopsy of the kidney, to demonstrate glomerular fat-embolism, is recommended in special cases—e.g., obscure post-traumatic coma.

My thanks are due to various clinical colleagues for their cooperation in studying the patients, and to Mr. R. Gill and Miss V. Montague-Smith, of the photographic department, for the illustrations.

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"The lack of general awareness that as a community we are a good deal less than reasonably efficient in the social sense is extremely disturbing. We are concerned at the loss of 3,500,000 working days through industrial disputes, but a loss of 28,000,000 working days through various forms of mental illness seems to cause no disquiet. We are appalled by the fatal road accident rate, but the equal incidence of suicide is the concern of no Minister."—G. C. JOHNSON. *Listener*, Sept. 22, 1960, p. 451.

NATURE OF ESSENTIAL HYPERTENSION

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The notion that high blood-pressure without evident cause in middle age is merely the tail end of the distribution of blood-pressure in the population is an interesting and important one (Hamilton et al 1954b, Pickering 1955, Oldham et al. 1960) However, to our mind there is little evidence in favour of it and much against it.

"*Low*" *or* "*Physiological*" *Levels of Blood-pressure*

It seems likely that the level of blood-pressure in healthy people *is* a graded characteristic—i e, it is continuously distributed, probably in a symmetrical, "normal" way It is also likely that inheritance plays a small part in setting the pressure of an individual and that the nature of the inheritance is multifactorial The evidence for this is provided by the surveys of Miall and Oldham (1955, 1958) on random samples of the population, these surveys showed that there is a highly significant relationship between casual pressures in subjects and in their first-degree relatives This is expressed by regression coefficients of 0 22 for systolic and 0 18 for diastolic pressures, which mean that, for every 10 mm. Hg that pressures of subjects are above or below the average, the mean pressures of their relatives will be approximately 2 mm. above or below average respectively These results, being representative of a total population, are based predominantly on subjects with low, as opposed to high, pressures 24 in a total of 612 subjects had diastolic pressures greater than 100 mm Hg, and of these only 12 had pressures higher than 110 mm Hg

Are There Two "*Populations*"?

The crucial question is whether people having high blood-pressure without evident cause, particularly in middle age (essential hypertension), are merely the tail end of the physiological or normal distribution of pressure, or whether they can be shown to form a qualitatively distinct group—a separate "population"

There is abundant evidence that no clear-cut dividing-line between physiological levels and essential hypertension can be found If there were such a division, there would be no controversy Distributions of pressures in the population are thus "continuous", in the sense that there is no break between low and high pressures However, as discussed earlier (Morrison and Morris 1959), it has been shown (Harris and Smith 1949) that such distributions by no means preclude the presence of two or more distinct "populations" Platt (1960) has illustrated how a combined frequency distribution of two distinct but overlapping distributions can produce a "continuous" curve The examination of general population samples, therefore, is unlikely by itself to determine whether these are homogeneous or include overlapping distributions that represent more than one "population" But the absence of a dividing-line in such distributions is not an argument for the theory of continuous variation—it is simply negative What it does mean is that some other way of classifying individuals is necessary if it is suspected that two separate populations are present Similar problems have been met in biochemical genetics (Harris et al. 1960)

Evidence for Two Populations

One way of testing the hypothesis that there are in fact two distributions is to examine relatives of hypertensives According to the single gene hypothesis, they should segregate into hypertensives and normotensives in roughly equal proportions, with such a high proportion of hypertensives the distribution should indicate the presence of two populations by being bimodal. Platt (1959) carried out such a test by plotting the pressures of middle-aged sibs of middle-aged hypertensives from the data of Hamilton et al. (1954b) and of Sobye (1948) In both sets of data the sibs showed a bimodal distribution of pressures—though it does appear that observer bias helped to produce it in Sobye's The systolic pressures of middle-aged sibs of hypertensives in the data of Weitz (1923) also show bimodality The only study which does not clearly produce a bimodal distribution among sibs of hypertensives is that of Oldham et al (1960) *

We used a different method of analysis with data on busmen. Whatever else might be in question, two things are widely accepted about essential hypertension first, that it shortens the expectation of life, and, second, that a hereditary factor of some kind is concerned in its development. If therefore we divide a given population into those whose parent(s) die in middle age and those whose parents live to old age, we shall have made use of these factors, heredity and premature death, to obtain one group containing more individuals with high blood-pressure and one containing less If the parents who die prematurely include a large proportion with essential hypertension, there should then be a large enough proportion of hypertensive sons to indicate segregation into normotensives and hypertensives by the appearance of bimodality in the distribution of blood-pressure among the sons In our investigation of busmen this was a long shot—but it came off The drivers whose parent(s) died in middle age showed a bimodal distribution of blood-pressure, whilst the remainder did not.

Thus in groups selected by the inheritance factor, bimodality—signifying the presence of two populations, one hypertensive and the other normotensive—has been found every time it has been looked for, with a single possible exception Attempts to explain away these findings (Pickering 1959a, Oldham et al 1960) are understandable but unhelpful.

Objections (Oldham et al. 1960) have been levelled at our method of selective analysis on the ground that hypertension is commoner among those who die over 65 than among those who die before this age. Figures were given in support of this objection showing (1) that deaths from cardiovascular and cerebrovascular diseases "commonly associated with hypertension" form a higher proportion of all deaths after 65 than before this age, and (2) that casual systolic pressures over 160 mm. Hg are common over the age of 65 and increase steadily in frequency as age advances The first objection is beside the point. We are comparing groups where, on the one hand, a parent died in middle age and, on the other hand, both parents survived to at least 65 Data from the national necropsy survey (Morris and Crawford 1958) show that the proportion with essential hypertension at necropsy in middle-aged men (45–64) was as follows in deaths from injuries, infections,

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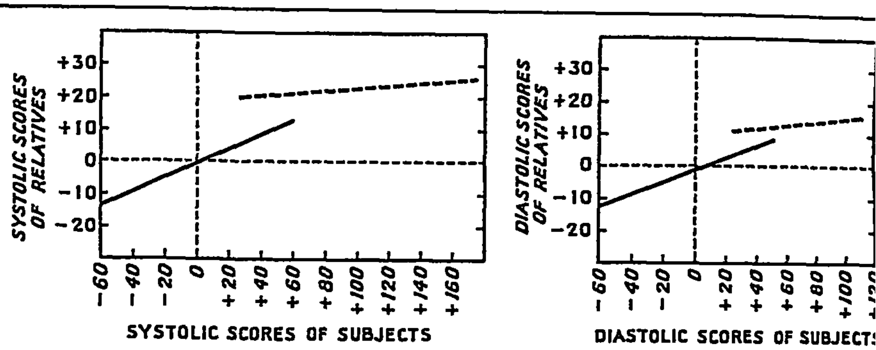
* Oldham et al quote data from the [illegible] random samples of Miall and Oldham (1955, 1958) The figures are curious, however, since they include "64 sibs aged 45–59 derived from propositi aged 45–59 with diastolic pressures of 100 mm. Hg or above" Yet there are only 15 such propositi



– – – – – Regression lines at low pressure levels (Miall and Oldham 1958)

——— Regression lines at high (subjects with diastolic pressures above 110 mm. Hg) pressur levels (Hamilton et al. 1954b)

Fig. 2—Regression lines of relatives' scores on subjects' scores for subjects with low pressures an subjects with high

cancer, &c., 11%, in deaths from ischæmic heart-disease, 35%, in deaths from cerebrovascular disease, 65%, and in deaths from other remaining conditions, 36%. These are figures of severe hypertension, nearly all of fixed diastolic hypertension that produced left ventricular hypertrophy. Figures of blood-pressure in old age are scanty, but the surveys of Hamilton et al. (1954a) and Miall and Oldham (1958) show that, of men surviving to ages 65–69, only 8% had diastolic pressures higher than 110 mm. Hg and only 2% had pressures above 120 mm. The prevalence of high *systolic* pressures in old age can be safely used as an indicator only of the prevalence of arteriosclerotic rigidity of large arteries, *not of the prevalence of essential hypertension*.

In general, it may be said that if premature death of parents among these busmen is not an indicator of the inheritance factor in essential hypertension it is an indicator of something even more interesting. We have an open mind on this and are working on it.

We do not follow the figures of Oldham et al. on the age at death of parents of hypertensives. If these refer to the parents of middle-aged male hypertensives they certainly contradict ours. We hope to produce further information on this question.

Resemblance Between Relatives

If the theory of continuous variation and multifactorial inheritance applies to "essential hypertension"—as it almost certainly does to physiological levels of pressure—the degree of resemblance between relatives will be the same at high levels of pressures as it is at low. That this is the case is, in fact, repeatedly claimed (Pickering 1959a and b, Miall and Oldham 1955, 1958, Oldham et al. 1960). The resemblance, using "sex and age-adjusted scores",† is said to be measured by a regression of a little over 0·2 among those with high pressures, which is very similar to the regressions calculated by Miall and Oldham for those with low pressures. However, this figure of a little over 0·2 is usually derived from calculations that are quite irrelevant to the question of the multifactorial inheritance of a graded character. When the regression coefficients for hypertensives and their relatives are calculated correctly, like those of Miall and Oldham (and of Galton), they are 0·05 for systolic and 0·06 for diastolic scores. These regressions are not significant. (Of course, the scores of relatives are on average raised as would be expected on any genetic hypothesis.) Fig. 1 shows the diastolic scores of subjects and the corresponding average scores of their relatives (adapted from table VI of Hamilton et al. 1954b). The first and last points manifestly do not "belong" with the others, but their exclusion makes little difference to the regressions. Moreover, what little interest there is in these regressions of 0·05 and 0·06 depends heavily on subjects with diastolic pressures just over 100 mm. Hg—i.e., just the group most likely to include subjects from the high end of the physiological distribution. If these subjects and their relatives are excluded, the regressions become rather less than 0·04 for both systolic and diastolic pressures, these regressions are significantly different from those of Miall and Oldham (1958). Thus the data indicate that at high levels of pressure there is little if any graded relationship between the height of the pressure in individuals and in their first-degree relatives.

Fig. 2 illustrates the regression lines of Hamilton et al. for a population with high pressures and those of Miall and Oldham for a population overwhelmingly with low pressures. There appears to be a clear break in continuity—evidence that the mode of inheritance at high levels differs from that at low, again indicating that there are two qualitatively different populations.

Rise of Blood-pressure in Middle Age

The next test of the hypothesis that there are two "populations" is to consider the common finding that average blood-pressures of population samples increase with age (e.g., Buchan et al. 1960). Is this due to a general increase among individuals as they pass through middle age, or is it largely due to the emergence of a special population with a special disease—those developing essential hypertension? Until relatives of hypertensives and of others can be followed *as individuals* through middle age it will be impossible to give a definite answer. But

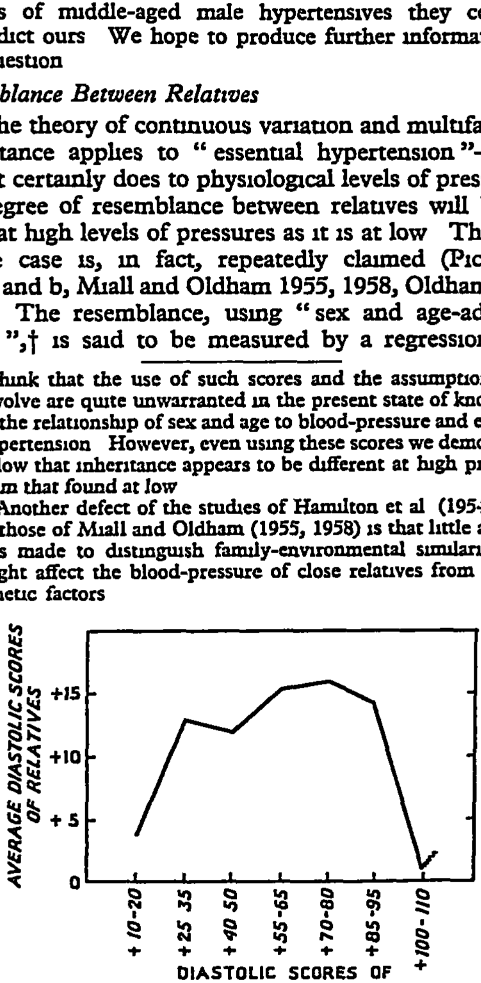


Fig. 1—Diastolic "sex and age-adjusted scores" of subjects with corresponding average scores of their relatives (adapted from table VI, Hamilton et al. 1954b)

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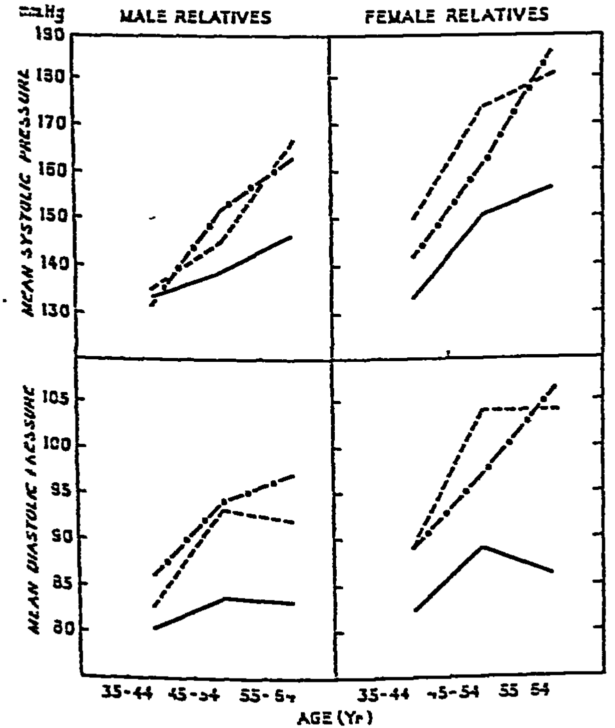
† We think that the use of such scores and the assumptions they involve are quite unwarranted in the present state of knowledge of the relationship of sex and age to blood-pressure and essential hypertension. However, even using these scores we demonstrate below that inheritance appears to be different at high pressures from that found at low.

Another defect of the studies of Hamilton et al. (1954b) and of those of Miall and Oldham (1955, 1958) is that little attempt was made to distinguish family-environmental similarity that might affect the blood-pressure of close relatives from strictly genetic factors.

group comparisons can give a strong hint. Fig 3 compares the rise of average pressures among relatives of normotensives and relatives of hypertensives. We have used data of relatives of normotensives of all ages and, following Platt (1959), relatives of middle-aged hypertensives. The relatives of hypertensives, as expected on the hypothesis that a large proportion of them will become hypertensive during middle age, show a significantly greater increase with age than the relatives of normotensives (see accompanying table). If they form any sizeable fraction of the population, hypertensives and their families must surely contribute very disproportionately to the rise of average blood-pressure that is found during middle age. In normotensive families, diastolic pressures scarcely rise at all, but women in such families do show a pronounced rise of *systolic* pressures. Since numbers are very small, Sobye's data are also shown on the figure—they behave very like those of Hamilton et al.

Bus drivers also show that the rise in average pressures is mainly seen in hypertensive families.

Among men with a parent who had died early we found indications of a bimodal distribution of systolic pressures at ages 45–54, and at 55–60 a clearly bimodal one with normotensive and hypertensive peaks. In both age-groups the distribution of pressure among those whose parents lived to old age was unimodal. The peaks of the bimodal distributions among sons with a parent who died early corresponded closely at the two ages. The rise of blood-pressure during middle age among drivers was almost confined to men with a parent who died early, and it was produced by the much higher proportion of men found in the second hypertensive peak of the bimodal distribution at 55–60 than at 45–54 (Morrison and Morris 1959).



—●—●— Relatives of normotensive subjects (Hamilton et al 1954b)

——— Relatives of middle-aged hypertensive subjects (Hamilton et al. 1954b)

- - - - - Relatives of middle-aged hypertensive subjects (Sobye 1948)

Fig 3—Rise of mean pressures with age among relatives of middle-aged (45-64) hypertensive subjects and among relatives of normotensive subjects.

RATE OF RISE OF PRESSURE WITH AGE IN RELATIVES OF HYPERTENSIVES AND RELATIVES OF NORMOTENSIVES (mm. Hg PER 10 YEARS OF AGE*)

Pressure	Sex	Relatives aged 35–64 of middle-aged† hypertensive subjects	Relatives aged 35–64 of normotensive subjects
Systolic	M	16·7 (53 men)	7·3 (93 men)
	F	17·7 (93 women)	11·4 (122 women)
Diastolic	M	5·1	1·5
	F	5·5	2·9

Combining probabilities in the two sexes, the differences between relatives of hypertensives and relatives of normotensives are significant ($p<0·05$) for both systolic and diastolic pressures.

* Data of Hamilton et al. 1954b

† Middle-aged = 45–64 years

Other analyses of pressures are now being made—e.g., following Perera (1960). All this is suggestive evidence once more that there are two populations.‡

Keen and Rose (1959) criticised our analyses by suggesting that parents who died prematurely include two groups, one with low blood-pressure and the other with high, that each of these is producing in the sons a unimodal distribution, and that when these are amalgamated an artefact bimodal curve in the sons is the result. If this criticism is valid, the proportion of hypertensive deaths among the parents of sons aged 45–54 must have been much smaller than that among parents of sons aged 55–60 since the proportion of hypertensive drivers is much lower at 45–54 than at 55–60. Our data on cause of death are meagre, but there is no evidence whatever of such a difference. It may be added that fig 1 of Keen and Rose ignores the age factor and contains errors of plotting and smoothing.

Conclusion

There does not seem to be any evidence on which to base a New Theory of essential hypertension. On the contrary, what evidence there is (and it is far from perfect) suggests that the common high blood-pressure without evident cause in middle age is qualitatively different from normal blood-pressure. Moreover, these cases of essential hypertension behave so homogeneously that it is reasonable to postulate they consist predominantly of a specific disease entity.

Future Work

One of the main conclusions of the Symposium on the Pathogenesis of Essential Hypertension (1960) held in Prague was that more knowledge about the natural history of the disease is urgently needed. In seeking this knowledge, there is clearly a place for epidemiological studies of complete populations (Morris 1957), and these studies must be prospective. They should be on an adequate scale: none of the studies we have been quoting is large enough satisfactorily to settle the issues that have been raised. For example, such studies should include large enough numbers of middle-aged subjects and their middle-aged relatives to allow separate analysis of actual pressures in the two sexes, thus obviating any need for "sex and age-adjusted scores", and the studies should be designed to avoid observer bias.

One difficulty of population studies is what measure of blood-pressure to use. Is the casual pressure a meaningful indicator of average pressure during daily life, or should some attempt be made to measure basal pressures (Smirk 1957)? Furthermore, in cases of intermittent hypertension, what pressure is to be used as the index for family studies? Much work is needed on these elementary questions In our studies of busmen (Kagan 1960) several pressures were taken during the course of a $1^1/_2$ hour examination, and these are now being analysed in relation to the casual pressure

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‡ The demonstration by Oldham et al. that, after following up a large number of people for four years, two populations in respect of the rise of pressure with age were not revealed, does not help. Some kind of genetic analysis seems to be necessary to disclose these two populations.

There is much scope for international studies of blood-pressure Oldham et al have pointed out the similarity between mean pressure values in Britain, in farm workers in the U S A, and in tea workers in Assam It is even more interesting that notable differences in mean values have been found between British studies and others For example, male Fijians and Indians in Fiji (Lovell et al 1960) and Africans in East Africa (Williams 1941) show little if any rise of pressure during middle age, while some Indians in India show only slight increases (Chopra et al 1942)

There is one particularly important area for study—the zone of overlap between the high end of the normal distribution and the low end of essential hypertension We have found, in two independent sets of data, a suggestion (numbers are too small to say more) that there may be a different relationship between systolic and diastolic pressures among men from " hypertensive " families and men from " normotensive " families in this zone of overlap Other analyses of the relationships are now being made Until this zone is clarified there will continue to be many definitions of " hypertension " But surely this is unimportant—difficulty in defining it does not mean that there is no specific disease

We are grateful again to our friends and colleagues for much help In particular, we wish to thank Prof Harry Harris and Prof Clifford Wilson

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" The widening gap between the general practitioner and the hospital specialist has received much publicity in lay as well as medical circles, but a second fissure is opening—one which bids to be just as wide and just as lamentable in its consequences I refer to the divorce between the bedside clinician and the clinical scientist There is no basis in fact for division of our profession into an intelligentsia of investigators and a peasantry of practitioners Research and the bedside practice of medicine indeed demand different talents, but each requires for success mental endowments of comparable quality "—Prof I G W HILL, *Scot med J* 1960, 5, 397

PULMONARY EMBOLISM

A STUDY OF LATE PROGNOSIS

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A PULMONARY embolus may cause rapid death Those patients who survive the initial catastrophe are usually expected to recover completely, though it is recognised that very occasionally pulmonary hypertension ensues (Magidson and Jacobson 1955, Wood 1956) A clinical impression that much disability often persists led to a follow-up study of patients with pulmonary embolism, no investigation of late prognosis after pulmonary embolism has been reported

Clinical Material

All patients diagnosed as having pulmonary embolism at the Central Middlesex Hospital in the three years 1957-59 were reviewed There were 136 patients (75 women and 61 men) in whom the diagnosis was satisfactorily substantiated 65 died immediately or within a few hours

Of the 71 survivors, 58 were seen personally 4 for reasons such as age or distance were not seen, but information about their progress was recorded in outpatient notes, and follow-up information was also available about 6 who had subsequently died Full information was not obtained about 3 of the 71 patients 1 had died, 1 had moved, and 1 refused to attend hospital

The follow-up, then, concerns 68 patients—33 women and 35 men The mean interval between the pulmonary embolism (or the first incident if recurrent) and the follow-up was 17 6 months

The average age of the 136 patients was 63 6 years In other series there has been a similar high average age, Barnes (1937) for instance, found that 93% of his patients were over 40 years of age

Embolic Episodes

Secondary Infection

Secondary staphylococcal infection occurred in 6 of the patients, 2 of these, with resistant strains, were extremely ill with abscess formation (Elliott, Gresham, and Phear 1960) but recovered although left with some disability In a further patient with a severe chest infection, who died despite tetracycline treatment, a resistant staphylococcus was probably present though no sputum culture was obtained In 1 patient pyopneumothorax due to *Clostridium welchii* developed, and in 2 patients a pneumococcal infection

Arrhythmia

At the time of the embolism 1 patient had transient auricular fibrillation and another transient auricular flutter, both recovered completely In 8 patients auricular fibrillation developed at the time of the embolism and persisted

Recurrent Embolism

12 patients had recurrent embolism The average interval between emboli was 2 6 years in the 6 patients with varicose veins, and 1 1 years in the remaining 6 patients with deep venous thrombosis

Late Prognosis

Of the 68 survivors, reviewed after an average interval of 17 6 months, 42 had recovered completely after the embolism 7 reported slight dyspnœa, 9 complained of moderate dyspnœa, and 1 of these had persistent auricular fibrillation 10 patients were severely disabled, and it is these patients I wish particularly to describe

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Of the 10 patients (6 women and 4 men) with severe persisting symptoms 7 had had clinically recurrent embolism. Before the onset of embolism all 10 had been well and active for their age. In only 1, a man with symptomless mitral incompetence, was there known previous heart or lung disease. Afterwards, 3 were in gross heart-failure and died, while in the rest heart-failure was controlled with varying success. Exertional dyspnœa and fatigue were notable. The average age of these 10 patients (67·0 years) was higher than that of the 9 patients with moderate dyspnœa (64·3 years) and of the completely recovered patients (52·6 years).

Of the 10 patients, 2 presented a clear picture of pulmonary hypertension and right ventricular failure.

Case 1.—A West Indian woman, aged 25, was delivered normally of a healthy boy on Feb. 2, 1958. Both the pregnancy and the puerperium were uneventful, and examination revealed no abnormal signs at this time, with no evidence of heart-disease or phlebitis. She had had 2 previous pregnancies (in 1951 and 1954) and in the second thrombosis of the right femoral vein had developed.

The patient was readmitted on June 2, 1958. For three months she had noticed increasing fatigue and dyspnœa, with loss of appetite and weight. For two weeks she had had cough with hæmoptysis and right pleural pain. On examination she was extremely ill and dyspnœic. The pulse-rate was 112 per minute with venous pressure raised 7 cm. and sacral œdema. There was a pulmonary systolic thrill and loud murmur, with normal pulmonary second sound. A pleural rub was heard in the right axilla. A chest radiograph showed a normal heart. The lung fields were clear apart from a small opacity in the right upper zone (fig. 1). An electrocardiogram showed right ventricular strain (fig. 2).

The patient remained very breathless and died suddenly on June 5, 1958. Postmortem examination showed both main pulmonary arteries to be blocked by adherent thrombus several weeks old. There was an infarct in the right lower lobe and thrombosis of the right femoral and calf veins.

Case 2.—A man, aged 72, was admitted in September, 1955, having had dyspnœa for three weeks and right pleural pain and hæmoptysis for four days. He had had large varicose veins for twenty years, but no recent phlebitis. He was afebrile, with râles and a pleural rub at the right lung base. An electrocardiogram showed small R waves with T-wave inversion in lead V_1 but no other abnormality. Pneumonia was diagnosed.

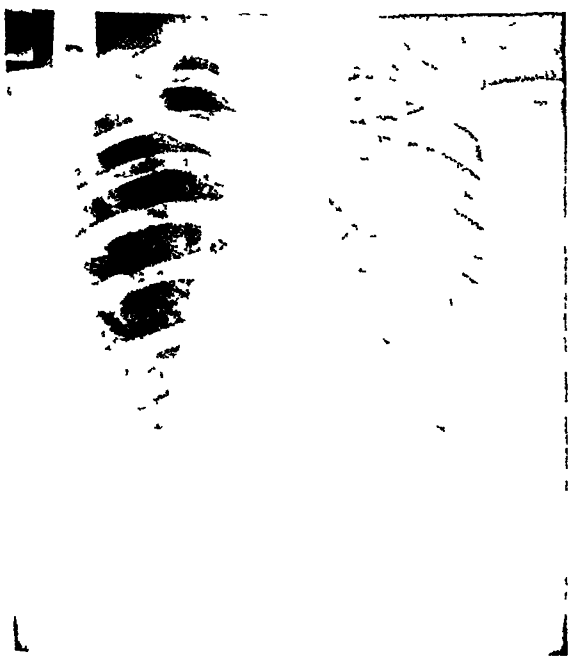

Fig. 1—Case 1: chest X-ray, showing opacity in right upper zone.

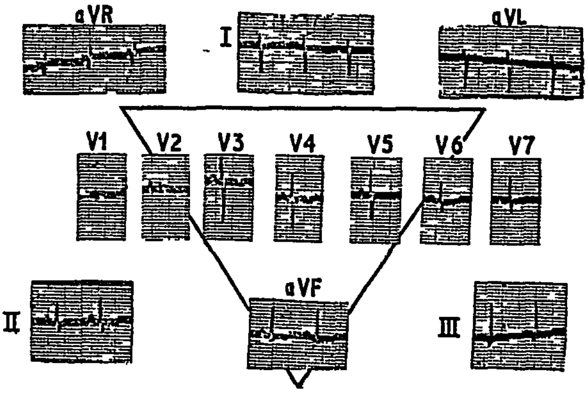

Fig. 2—Case 1: electrocardiograph, with changes indicating right ventricular strain.

The patient recovered, but from December, 1957, noticed increasing exertional dyspnœa and fatigue. When he was readmitted in September, 1959, there was no orthopnœa, but he could walk only very slowly on flat ground and was breathless on dressing. Examination showed cyanosis, regular cardiac rhythm, and gross congestive heart-failure with systolic venous pulsation to the jaw. The heart was enlarged with a tapping impulse. A loud tricuspid systolic murmur was heard, and in the pulmonary area there was a high-pitched systolic murmur with accentuated pulmonary second sound. A chest radiograph and screening showed right sided cardiac enlargement with prominent main pulmonary arteries which pulsated poorly (fig. 3). An electrocardiogram (fig. 4) confirmed right ventricular hypertrophy.

The heart-failure was controlled. Treatment with anticoagulants continues, so far without much improvement.

In all the remaining 8 patients there was clinical evidence of right ventricular hypertrophy, the pulmonary second sound was accentuated without loud pulmonary murmurs, and in 3 a third heart sound was heard. Auricular

Fig. 3—Case 2: chest X-ray, showing right-sided cardiac enlargement and prominent main pulmonary arteries.

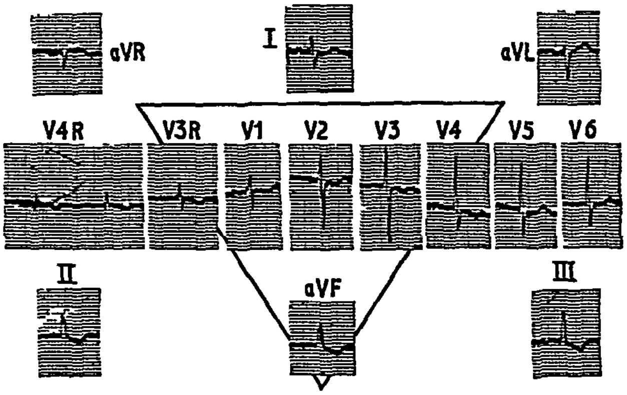

Fig 4—Case 2 electrocardiograph, with changes indicating right ventricular hypertrophy

fibrillation was present in 7 of the 8 Chest radiographs and screening showed generalised cardiac enlargement, predominantly affecting the right ventricle Electrocardiograph evidence of right ventricular hypertrophy was present in 5 of the 8 The emboli had arisen from longstanding varicose veins in 4 cases, and from thrombophlebitis in the remaining 6 Pulmonary embolism was recurrent in 7 patients, with periods of 3 months to 5 years (average 23 3 months) from first to latest recurrence

In addition to case 1 (see above) 2 patients died A postmortem examination was carried out on 1 of these, confirming the diagnosis

Case 3 —A woman, aged 83, was admitted in November 1958 For many years large varicose veins had been present, and she had been known to be hypertensive for ten years Over the previous year dyspnœa and angina pectoris had developed Examination showed auricular fibrillation, with blood-pressure 185/95 mm Hg, a thrombosed vein in the right calf, and an infarct at the base of the right lung

The patient improved but was readmitted in January, 1959, with increasing dyspnœa There was now severe congestive heart-failure, and she died Postmortem examination showed multiple emboli in the small and medium pulmonary arteries There was moderate left ventricular hypertrophy, and the coronary arteries were patent though narrowed in places to half the normal lumen

Of the 10 patients with severe dyspnœa, 3 are now receiving prolonged anticoagulant treatment Progress is satisfactory in 2, but there has been no improvement in the 3rd (case 2) 3 patients are dead 1 patient, who had two emboli over a five-month period, has had no recurrence over a further eighteen months 3 patients had single emboli fifteen months, sixteen months, and eighteen months before review

Discussion

This study suggests that severe disability may often result from pulmonary embolism Of the 68 survivors reviewed, 10 had persistent troublesome symptoms and a further 9 remained moderately dyspnœic In 2 patients pulmonary hypertension with right-ventricular failure was clearly present In the remainder with severe dyspnœa, myocardial ischæmia may have been partly responsible, though there was no previous disability Established auricular fibrillation followed the embolism in 8 patients with severe or moderate symptoms and may have been an important contributory factor In contrast, Owen et al. (1953) found that their 12 patients presenting with unexplained right-sided heart-failure were in sinus rhythm The absence of many of the classical features of pulmonary hypertension does not exclude pulmonary obstruction, for several workers have reported dyspnœa, fatigue, and cough long before right ventricular hypertrophy was recognisable (Petch 1951, Owen et al 1953, Ball et al 1956)

Occlusion of the pulmonary arterioles by multiple or recurrent emboli is an accepted cause of chronic right-sided heart failure but is usually thought to be rare (Ljungdahl 1928, Barnes and Yates 1929, Belt 1939, Covey 1943, Carroll 1950, Petch 1951) Wood (1956) describes only 5 cases These patients may present with venous thrombosis and acute embolic episodes Sometimes, unexplained right ventricular hypertrophy and failure develop (Owen et al 1953, Davison et al 1956) The diagnosis is often made only at necropsy (Belt 1939)

Obstruction of the main pulmonary arteries by massive thrombus is also diagnosed more often postmortem than in life (Schein et al 1958) The condition may well be commoner than is suspected, for Zollinger and Hensler (1958) found 68 cases of longstanding massive embolic obstruction in 4000 necropsies Full clinical details were available in 14 of their patients, in only 3 of whom had the diagnosis been suspected in life Heart-failure in the remaining 11 patients was usually attributed to myocardial ischæmia The majority of these massive occlusions are due to pulmonary embolism rather than thrombosis in situ, though no certain decision is possible in the absence of a history of phlebitis or embolus Thus, Ball et al (1956) thought that 16 of their 23 cases were embolic

The clinical picture of pulmonary-artery obstruction is characteristic

Exertional dyspnœa is predominant, often without orthopnœa There may be a dry cough Recurrent pleural pain and hæmoptysis occur, in association with recurrent emboli Patients complain of tiredness and may faint, especially on exercise (Ball et al 1956, Davison et al 1956) Physical signs include cyanosis, a small pulse, and right-ventricular hypertrophy The venous pressure may be raised, sometimes with tricuspid incompetence The pulmonary second sound is normal or soft, with a pulmonary systolic murmur due to partial occlusion of the main pulmonary artery (Owen et al 1953) A peripheral source of emboli is often recognised Radiologically, there is enlargement of the right side of the heart The main pulmonary arteries are large but pulsate poorly, and the peripheral lung fields are clear because of oligæmia (Shapiro and Rigler 1948, Hamelin and Eyer 1951) The electrocardiogram confirms right ventricular hypertrophy (Carroll 1950, Owen et al 1953, Ball et al 1956, Wood 1956)

Early diagnosis is important, so that anticoagulant treatment may be started before irreversible pulmonary hypertension develops (Wood 1956) Many characteristic features may be absent in the early stages, and early diagnosis depends much on clinical suspicion Other causes of right ventricular hypertrophy and failure must be considered Right ventricular failure secondary to respiratory disease is excluded by the absence of chronic chest infections Mitral stenosis, atrial septal defect, and pulmonary stenosis must be considered (Ball et al 1956) Pulmonary angiography may be helpful (Carroll 1950)

Long-continued anticoagulant treatment proved valuable in 2 cases (Davison et al 1956, Wood 1956), and 2 of the present series have improved with anticoagulants Initial rest helps to reduce pulmonary hypertension If emboli still recur, ligation of the inferior vena cava may be needed The frequency of severe persisting symptoms in the present group suggests that protracted anticoagulant treatment after pulmonary embolism would often be justifiable

Summary

136 cases of pulmonary embolism were diagnosed in an 800-bed general hospital over three years 71 patients survived the embolism, and 68 of these were reviewed after an average period of 17 6 months

10 had severe persisting disability, 2 with obvious pulmonary hypertension 9 others had moderate persisting dyspnœa

With embolic pulmonary-artery obstruction anticoagulants should be started at once in order to prevent irreversible pulmonary hypetension

I am grateful to the physicians and surgeons of the Central Middlesex Hospital, especially Dr Horace Joules and Dr Keith Ball, for help and for permission to study their patients I thank Dr Arthur Willcox for advice in the preparation of this paper

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ENZYME DEFICIENCY IN HÆMOLYTIC DISEASE OF THE NEWBORN

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THE susceptibility of red blood-cells to hæmolysis has been shown to be associated with certain inherited errors of metabolism within the cells Thus the hæmolysis in Negroes following primaquine therapy is associated with a lowered level of reduced glutathione in the red blood-cells, and when these cells are incubated in vitro with acetyl phenylhydrazine the level of reduced glutathione falls notably (Beutler et al 1955, 1957) These changes have been related to a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G-6-P D) in these cells (Carson et al 1956) This enzyme has also been shown to be deficient in patients in whom hæmolytic episodes have followed ingestion of sulphonamides, *p*-aminosalicylic acid, naphthalene, and *Vicia faba* (Sansone and Segni 1958, Szeinberg et al. 1958) This deficiency appears to be inherited as a sex-linked gene of intermediate dominance (Browne 1957)

In several recent reports of cases in which hæmolytic episodes have been associated with G-6-P D deficiency there was a history of neonatal jaundice

Such a history was obtained in the case of a 4-year-old Italian child who had a severe hæmolytic episode following sulphafurazole therapy (Newton and Bass 1958) There were similar histories in cases of children with relapsing hæmolytic anæmia associated with G-6-P D deficiency (Shahidi and Diamond 1959, Zinkham and Lenhard 1959) In the case of a 32-year-old Jewess in whom a severe hæmolytic episode following sulphamethoxypyridazine therapy was associated with G-6-P D deficiency, the patient gave a history of having lost 3 children with severe neonatal jaundice (Vella and Phoon 1959) Smith and Vella (1960) have examined blood specimens from 20 cases of hæmolytic disease in the neonatal period (19 Chinese and 1 Malay) unassociated with ABO or Rh incompatibility, and found G-6-P D deficiency in every case but 1

The following report deals with three Malay families in which there seems to be a strong association between neonatal hæmolytic disease and G-6-P D deficiency

Methods

Glucose-6-phosphate dehydrogenase deficiency was detected by the rapid colorimetric method of Motulsky and Campbell (cited by Vella 1959) The enzyme catalyses the reaction in which reduced triphosphopyridine nucleotide (TPNH) is generated

$$\text{Glucose-6-phosphate} + \text{TPN} = \text{6-phosphogluconic acid} + \text{TPNH} + \text{H}^+$$

The dye brilliant cresyl-blue, which is colourless in the reduced state, is used as an indicator of this reaction and the time taken for decolorisation under standard conditions is recorded in the test Enzyme deficiency has been confirmed by spectrophotometric method in blood samples which fail to decolorise in 120 minutes In all samples reported below as deficient, decolorisation had not occurred in 3 hours

All blood samples were examined for abnormal hæmoglobins by paper electrophoresis at pH 8 6 (veronal buffer) and pH 6 5 (citrate buffer)

Alkali-resistant hæmoglobin was estimated by the method of Chernoff (1955)

Case-records

FAMILY 1

The first member of this Malay family to be examined was a 4-day-old male infant

He was born on Dec 9, 1959, in the British Military Hospital, Singapore, at full term, delivery was normal and his birth-weight was 7 lb 2 oz The mother had been given no drugs during pregnancy or labour, and there was no history of her having sucked moth-balls (Zinkham and Childs 1958) The infant received no vitamin K or other drugs in the period immediately after birth He was breast-fed and thrived until the fourth day of life

On the fourth day he was noted to be jaundiced, and the jaundice rapidly deepened until the sixth day when kernicterus developed At this time there was moderate hepatosplenomegaly but no evidence of any focus of infection The jaundice slowly cleared over the next seven days, but the neurological signs have persisted Investigations at that time were as follows hæmoglobin 11 6 g per 100 ml , which fell to 6 0 g per 100 ml on the eighth day , white blood-cells 12,700 per c mm (polymorphs 54%, lymphocytes 42%, monocytes 3%, eosinophils 1%), reticulocytes 3%, serum-bilirubin 18 mg per 100 ml (indirect acting) Examination of a peripheral-blood smear revealed anisocytosis, poikilocytosis, normoblastosis, and no Heinz bodies The erythrocyte osmotic fragility was normal The direct and indirect Coombs tests were negative The infant's blood was type A, CDe CDe ($R_1 R_1$) and its mother type A, CDe/CDe ($R_1 R_1$) No incompatibility was demonstrated between the infant's cells and maternal serum at 4 C, room-temperature, or 37 C in either saline or albumin Liver-function tests showed thymol turbidity 3 units, zinc-sulphate flocculation 4 units, and alkaline phosphatase 19 2 King-Armstrong units The Wassermann reaction and Kahn test were negative The fæces contained stercobilin, and urine analysis revealed increased amounts of urobilinogen. There were no abnormalities of hæmoglobin on paper electrophoresis at pH 8 6 or pH 6 5, only hæmoglobins A and F being present. G-6-P D activity was estimated by the method outlined above, and the infant's cells were shown to be enzyme-deficient

For this reason family studies were done The parents were healthy and there were five siblings, two female and three male There was no history of consanguinity One male sibling had died of an obscure illness in his village, aged 9 months There were no abnormalities on physical examination of any of the family, and investigations of their blood showed normal levels of hæmoglobin and serum-bilirubin In no case was the reticulocyte-count greater than 1% of the total red-cell count There were no abnormalities of hæmoglobin at pH 8 6 or pH 6 5, and in all cases the level of alkali-resistant hæmoglobin was less than 2% G-6-P D deficiency was demonstrated in both parents and in one female and two male siblings (One male and one female sibling were not available for examination)

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FAMILY 2

This family consisted of the parents and two male children, both of whom were deeply jaundiced from the 3rd day of life until the end of the 2nd week In addition there had been four other pregnancies, the infants all having died, deeply jaundiced, between the fifth and the eighth day of life These infants had all been born at full term of normal deliveries and there was no history of the mother or infants receiving any drugs All the infants were males Two of them were seen in the British Military Hospital

The first of these two was a male child weighing 7 lb 2 oz who was born on Oct 28, 1958, of a normal delivery He thrived until the third day of life when he was noted to be jaundiced, there was no hepatosplenomegaly and no evidence of infection The jaundice rapidly deepened and the child died of kernicterus on the seventh day of life Investigations on admission (4th day of life) showed hæmoglobin 7 2 g per 100 ml, white blood-cells 14,300 per c mm (polymorphs 64%, lymphocytes 30%, monocytes 3%, eosinophils 3%) A peripheral-blood smear revealed anisocytosis, poikilocytosis, and normoblastosis Serum-bilirubin 10 mg per 100 ml (all indirect acting) Direct and indirect Coombs tests negative The infant's blood-group was type B, CDe/CDe (R_1 R_1), and the mother's type B, CDe/CDe (R_1 R_1) No incompatibility was demonstrated between the infant's cells and maternal serum at 4°C, room-temperature, or 37°C in either saline or albumin The urine contained increased amounts of urobilinogen Liver-function tests thymol turbidity 1 unit, zinc-sulphate flocculation 1 unit, alkaline-phosphatase 10 King-Armstrong units The Wassermann reaction and Kahn test were negative

The second child was a male weighing 5 lb at birth This child became deeply jaundiced on the 2nd day of life and died of kernicterus on the 5th day Investigations on the 4th day of life showed hæmoglobin 9 6 g per 100 ml A peripheral-blood smear revealed much anisocytosis, poikilocytosis, and normoblastosis Serum-bilirubin 17 mg per 100 ml (all indirect acting) Direct and indirect Coombs tests were negative This infant's blood was type B, CDe/CDe/ (R_1 R_1), and no incompatibility was shown between the infant's cells and maternal serum at 4°C, room-temperature, and 37°C in either saline or albumin The Wassermann reaction and Kahn test were negative

In view of these unexplained deaths the parents and two living children were examined There was no abnormality on physical examination, and investigations revealed normal level of hæmoglobin and serum-bilirubin Saline fragility tests were normal There were no abnormalities of hæmoglobin at pH 8 6 and pH 6 5, and in no case was the level of alkaline-resistant hæmoglobin more than 2% of the total hæmoglobin G-6-P D studies showed deficient enzyme activity in the father and two siblings and normal activity in the mother

FAMILY 3

The patient was a 4-year-old boy

He was born in a kampong (Malay village) of a full-term normal delivery, weighing at birth 5 lb 6 oz No drugs had been given to the mother or child. He was well until the 3rd day of life when he was noted to be jaundiced The jaundice deepened until the 6th day when he had several convulsions, and after this he lay in a position of opisthotonos for several days His jaundice cleared slowly over the next two weeks The child was slow to sit up and had never walked or talked. There had been no further episodes of jaundice

On examination the child was mentally and physically retarded The mucous membranes were pale, no hepatosplenomegaly The limbs were severely hypertonic, and pronounced athetosis was noted The history and findings pointed to the diagnosis of kernicterus with severe neurological sequelæ.

Investigations showed hæmoglobin 9 0 g per 100 ml, red blood-cells 3,350,000 per c mm, white blood-cells 10,100 per c mm (polymorphs 83%, lymphocytes 14%, monocytes 1%, eosinophils 2%) A peripheral-blood smear revealed microcytosis, anisopoikilocytosis, and occasional normoblasts Reticulocytes 3% Saline fragility test normal Direct and indirect Coombs test negative The child's blood was type O, cDE/cDE (R_2 R_2), and the mother's type O, cDE/cDE (R_1 R_1) No incompatibility was demonstrated between the child's cells and maternal serum at 4°C, room-temperature, and 37 C in saline or albumin Liver-function tests serum-bilirubin 1 mg per 100 ml, zinc-sulphate flocculation 2 units, thymol turbidity 3 units The urine contained a slightly increased amount of urobilinogen There was no abnormality of hæmoglobin at pH 8 6 or pH 6 5 Alkaline-resistant hæmoglobin was less than 2% Enzyme studies showed deficient G-6-P D activity in the red blood-cells The hæmotological findings suggested that this child had a low-grade hæmolytic process, though no acute episode had occurred since the neonatal period

Examination of the parents and one female sibling revealed no clinical or hæmatological abnormality There were no abnormalities of hæmoglobin on electrophoresis and G-6-P D studies showed normal enzyme activity One of the parents must have been a carrier for this deficiency Alving et al (1958) have pointed to the occasional discrepancy between in-vitro tests of enzyme deficiency and and in-vivo susceptibility to hæmolysis

FURTHER FAMILIES STUDIED

So far nine further Malay families have been studied In each of these families one or more infants were jaundiced from about the 3rd day until the 2nd week of life Unlike families 1–3 there was no evidence of a hæmolytic basis for this jaundice, and in no case was G-6-P D deficiency demonstrated in either the infant or any member of the family

Discussion

In the three Malay families described here G-6-P D deficiency was associated with severe hæmolytic disease in the newborn, resulting in kernicterus In each case ABO and Rh incompatibility, infection, and hæmoglobinopathy were excluded, and, so far as possible, drug sensitisation were also excluded This seems unlikely to be a chance association G-6-P D deficiency is not common in Malaya, Vella (1959) found no cases in blood specimens from 90 Malay blood-donors Hæmolytic disease is also uncommon, the cases described here being the only instances in 600 Malay births in the British Military Hospital, Singapore, between 1957 and 1959 (It is exceedingly rare to find a Rh-negative Malay)

The mechanism of the hæmolysis in these cases is uncertain Possibly a so-far unrecognised external sensitising agent is responsible, though this seems unlikely It seems more likely that, under certain circumstances, hæmolysis can occur without any such agent in patients with susceptible red blood-cells A history of neonatal jaundice is common in G-6-P D-deficient families, and possibly the normal stresses of the perinatal period are sufficient to cause hæmolysis in infants with susceptible cells. Further work is needed on this.

Summary

A history of neonatal jaundice is not uncommon in patients with a deficiency of glucose-6-phosphate dehydrogenase in their red blood-cells.

In three Malay families severe hæmolytic jaundice in the neonatal period was associated with deficiency of this enzyme. The mechanism is unknown.

I wish to thank Dr F. Vella, late of the department of biochemistry, University of Malaya, for performing the glucose-6-phosphate dehydrogenase studies on these patients, Captain R. D. Williams, R.A.M.C., for collecting blood specimens from several of the Malay families, Lieut.-Colonel J. P. Baird, R.A.M.C., and Major S. E. M. Jarvis, R.A.M.C., for their advice and interest in this work, and the command pathology laboratory, FARELF, for their cooperation.

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PROPHYLACTIC ISONIAZID IN NURSES IN A TUBERCULOSIS HOSPITAL

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TUBERCULOSIS as an occupational hazard in nurses has declined sharply in the United Kingdom (*Lancet* 1959). The King George V Hospital for tuberculosis has 1300 beds for non-European patients. Over 90% of adults have a positive sputum on admission. Two-thirds of patients have far-advanced pulmonary tuberculosis. The death-rate has declined in recent years, but 12·5% of patients die in hospital, half of these within a month after admission. Here the hazard remains

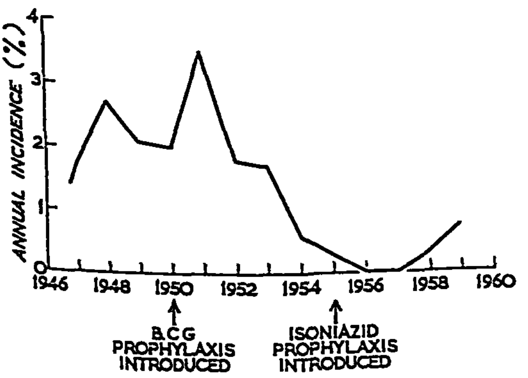


Fig. 1—Annual incidence of tuberculosis.

TABLE I—PREVALENCE OF TUBERCULOSIS ON APPOINTMENT (MAY 20, 1946, TO DEC. 31, 1958)

Race	Total X-rayed	No. with tuberculosis
Bantu		
Zulu	894	25 (*2·8%*)
Xhosa	479	10 (*2·1%*)
Other	151	3 (*2·0%*)
Total	1524	38 (*2·5%*)
Indian	211	3 (*1·4%*)
Coloured	112	1 (*0·9%*)
All races	1847	42 (*2·3%*)

X-ray results not known for 37 nurses (2·0%).

Wards in this hospital consist of 60-bed units. The nursing team comprises about 15 nurse-aides led by fully-trained nurses. Figures in this paper refer to the non-European nurse-aides only, of whom there were about 1900.

The first non-European nurse-aides were appointed to the staff on May 20, 1946. Young Bantu, Coloured, and Indian women who can read and write and have passed standard VI or VII are given a three-month elementary nursing course with a bias towards practice rather than theory (Dormer 1950). The nurse-aides then enter the wards, but continue to attend lectures for about eighteen months. Kindness to the sick, and the performance of simple actions which make sick people comfortable, are the basis of training.

The usual methods of control of tuberculous infection and early detection of cases among the staff are applied, including two-monthly to three-monthly X-rays, tuberculin-testing, and regular re-testing of negative reactors. In addition, B.C.G. prophylaxis was introduced in 1950, and isoniazid prophylaxis in 1955.

Findings

Annual Incidence of Tuberculosis

The annual incidence, which is taken as the number of cases expressed as a percentage of the mid-year establishment, is shown in fig. 1. Between May 20, 1946, and December, 1959, 55 cases of tuberculosis arose amongst non-European nurse-aides.

Prevalence of Tuberculosis on Appointment

The prevalence of tuberculosis on appointment is, in some degree, an indication of the amount of tuberculosis likely to develop later, as environmental factors may modify the attack-rate although exposure is constant. Thus, the Prophit survey (Daniels et al. 1948) found a higher prevalence of tuberculosis on entry among Irish and Welsh nurses (2·8%) than among others (1·1%), and also a higher morbidity-rate amongst Irish and Welsh

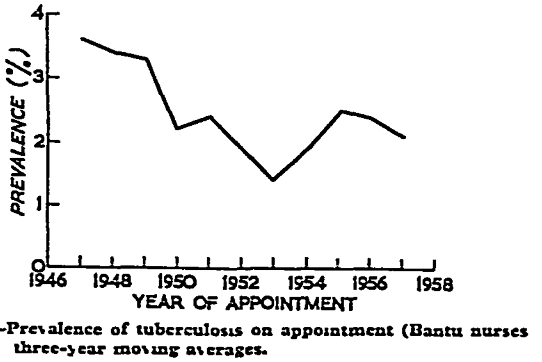


Fig. 2—Prevalence of tuberculosis on appointment (Bantu nurses only): three-year moving averages.

nurses (27 1 per 1000 years) than amongst others (10 7 per 1000 years)

The prevalence of tuberculosis on appointment of nurses in this series was 2 3% (table I) The prevalence has not changed much since 1950, but the higher figures of the early years have not been reached again (fig 2) It is improbable that changes in prevalence account for the lower incidence since 1955

Length of Service

The incidence of tuberculosis has been greatest in the second, third, and fourth years of service (fig 3) The structure of the staff as regards length of service does not account for the fall in incidence in recent years (fig 4)

Tuberculin Sensitivity on Appointment

The percentage of nurses tuberculin-positive on appointment was 83 9 (table II) A year-by-year analysis of these figures does not show a rising or falling trend (fig 5) The incidence of tuberculosis does not differ significantly according to whether the nurses were tuberculin positive or negative on appointment (table III) Over 80% of nurses who were tuberculin-negative on appointment and who did not receive B C G became tuberculin-positive within a year after appointment Nevertheless, of the 12 nurses who were initially tuberculin-negative and in whom tuberculosis developed, the lesions developed in only 3 at the time of conversion or soon after (table IV) The remaining 9 cases in initially tuberculin-negative nurses developed thirteen months to five years after conversion The majority of initially tuberculin-negative nurses thus became tuberculin-positive without developing detectable tuberculous lesions and may be regarded as augmenting the number of tuberculin-positive persons liable to develop tuberculosis In any event, the total number tuberculin-negative on appointment was small, and the major problem is control of tuberculosis among nurses who are already tuberculin-positive on appointment

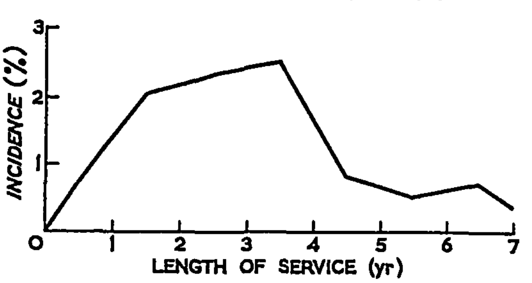
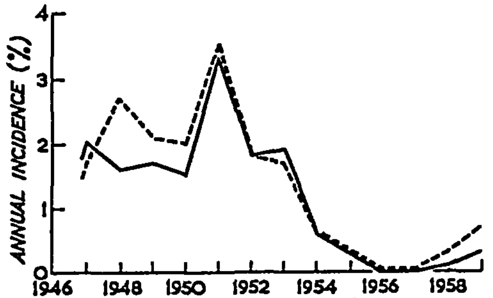


Fig 3—Incidence of tuberculosis related to length of service



——— Incidence (%) standardised for length of service against 1952

– – – – Incidence (%) crude figures as in fig 1

Fig 4—Annual incidence of tuberculosis related to length of service

TABLE II—TUBERCULIN SENSITIVITY ON APPOINTMENT (MAY 20, 1946, TO DEC. 31, 1958)

Race	Total known	No tuberculin positive
Bantu		
Zulu	876	730 (*83 3%*)
Xhosa	166	113 (*95 1%*)
Other Bantu	138	121 (*87 7%*)
Total	1180	1291 (*87 4%*)
Indian	205	129 (*62 9%*)
Coloured	110	83 (*75 5%*)
All races	1795	1506 (*83 9%*)

Tuberculin sensitivity not known for 89 nurses (4 7%)

B C G Prophylaxis

B C G, at best, could help only those originally tuberculin-negative—i e, 16% of the staff B C G was first given in 1950 to those members of the staff who had remained tuberculin-negative, and gradually those found negative on appointment were included in the scheme This procedure was followed until towards the end of 1955 when B C G vaccination was discontinued It was recommenced in the middle of 1959 In all, 83 nurses who were originally tuberculin-negative received B C G before the end of 1955, and tuberculosis developed in 3 of these (3 6%) (cases 1–3)

Isoniazid Prophylaxis

In September, 1955, isoniazid prophylaxis was introduced All nurses received isoniazid 300 mg daily in a single dose No case of tuberculosis was detected thereafter until April, 1958, when 1 case was detected, and 3 further cases occurred in 1959 (cases 3–6) Thus, of some six hundred nurses who have received isoniazid prophylactically, 4 have developed tuberculosis With isoniazid prophylaxis, the incidence of tuberculosis has fallen irrespective of tuberculin sensitivity on appointment (table V) Thus far, no case of tuberculosis has occurred in a nurse who was tuberculin-negative at the start of isoniazid prophylaxis (table VI) Given prophylactically, isoniazid has benefited both tuberculin-negative and tuberculin-positive nurses

TABLE III—INCIDENCE OF TUBERCULOSIS RELATED TO INITIAL TUBERCULIN REACTION

Tuberculin reaction of appointment	No of nurses	No of cases of tuberculosis	Incidence (%)
Positive	1506	42	2 8
Negative	289	12	1 2

The incidence was low in 1954 and 1955, before the

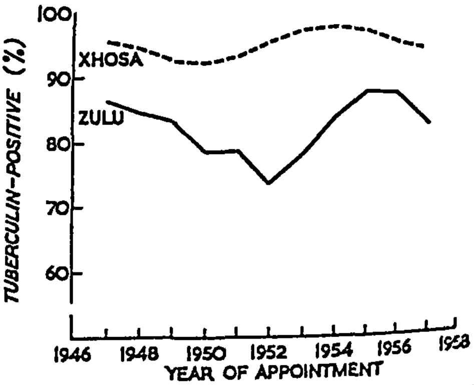


Fig 5—Tuberculin reaction on appointment: three-year moving averages.

TABLE IV—DATA ON 12 CASES OF TUBERCULOSIS IN NURSES WHO WERE TUBERCULIN-NEGATIVE ON APPOINTMENT

Time of conversion after appointment (mos)	Time between conversion and manifestation of tuberculosis	Type of tuberculosis	Time of conversion after B C.G administration
Under 3	1 13 mos 2 16 mos 3 22 mos 4 3½ yr 5 Over 5 yr	Generalised Minimal Minimal Minimal Moderate	2 mos (case 3)
3–6	6 Simultaneous 7 2 yr	Primary Minimal	
6–9	8 Simultaneous 9 17 mos	Minimal Pleural effusion	
9–12	10 18 mos	Minimal	
12–15	11 2–3 mos 12. 17 mos	Pleural effusion Minimal	1 yr (case 2) 6 weeks (case 1)

introduction of isoniazid prophylaxis Although these figures are unexpected, the number of cases involved in each year is small, and the low 1954 and 1955 figures may represent chance fluctuations After the introduction of isoniazid prophylaxis, no case occurred for two and a half years The crop of cases in 1959 is disappointing

It is noteworthy that of the 4 cases of tuberculosis that arose after the introduction of isoniazid prophylaxis, 3 were detected while the nurse was on leave or within a month of her return from leave It is fairly certain that nurses did not continue taking isoniazid while on leave, and not impossible that an infection kept at bay by isoniazid flared up on withdrawal of the drug Of the 51 cases that occurred before the introduction of isoniazid, 7 (13 7%) were detected while the nurse was on leave or within a month after her return from leave This is the expected proportion in twenty days' leave plus thirty days—i e , 50/365=13 7% Accordingly, nurses are now urged to continue taking isoniazid while on leave, and also for three months after leaving the staff

TABLE V—INCIDENCE OF TUBERCULOSIS RELATED TO TUBERCULIN SENSITIVITY ON APPOINTMENT AND ISONIAZID PROPHYLAXIS

Prophylactic isoniazid	Tuberculin-positive on appointment		Tuberculin-negative on appointment	
	Total	No of cases of tuberculosis	Total	No of cases of tuberculosis
Nil	1365	39 (*2 9%*)	214	11 (*5 1%*)
Prophylaxis during part or all of service	*569*	3 (*0 5%*)	*93*	1 (*1 1%*)

TABLE VI—INCIDENCE OF TUBERCULOSIS RELATED TO TUBERCULIN SENSITIVITY ON APPOINTMENT AND AT START OF ISONIAZID PROPHYLAXIS ON SEPT 20, 1955

Date of appointment	Tuberculin reaction on appointment	Subsequent tuberculin reaction	Tuberculin-positive		Tuberculin-negative	
			Total	No of cases of tuberculosis	Total	No of cases of tuberculosis
Before Sept. 20, 1955	Positive		287	2 (*0 7%*)		
	Negative	Negative on Sept. 20, 1955			7	
		Positive after B C.G	28	1		
		Positive without B.C.G	16			
After Sept. 20, 1955			282	1 (*0 4%*)	42	
Total			613	4 (*0 7%*)	49	

Case-records

Case 1—A nurse, aged 18 on appointment in June, 1949, was repeatedly tuberculin-negative between then and January, 1950 On April 14, 1950, B C G was given, and on June 2, 1950, she was shown to be tuberculin-positive On Nov 24, 1951, X-ray showed slight tuberculous density in the first right interspace, the sputum contained *Mycobacterium tuberculosis* The condition responded well to treatment with streptomycin and *p*-aminosalicylic acid (P A S) On Sept 21, 1954, the patient was well, and the lesion quiescent.

Case 2—A nurse, aged 17 on appointment in March, 1950, was twice that month shown to be tuberculin-negative. B C G was given on April 14, 1950 On May 22, 1951, she was found to be tuberculin-positive. On Aug 2, 1951, X-ray examination showed a pleural effusion All investigations for *Myco tuberculosis* were negative The disorder responded well to treatment with streptomycin and P A.S In November, 1959, the patient was still on the staff, fit, with X-ray clear

Case 3.—A nurse, aged 21, was tuberculin-negative on appointment in September, 1952 Next month B C G was given, and two months later she was tuberculin-positive On Sept 20, 1955, isoniazid prophylaxis was started, and the drug was taken regularly except for periods of leave, the last of which was from March 8 to 30, 1958 On April 9, 1958, X-ray showed early infiltration and cavitation of left apex Direct and cultural examination of sputum was positive for *Myco tuberculosis* The organisms were insensitive to isoniazid at concentrations of 5 to 200 µg per ml. of medium On guineapig inoculation the organism caused enlargement of mesenteric nodes and a few foci in the liver—virulence grading 5/18 The patient was treated with 'Dipasic' (isoniazid and P.A.S) 60 mg per kg , streptomycin 1 g daily for thirty days then bi-weekly, and prednisone In four months the X-ray showed much improvement, and in six months the sputum was negative On Nov 1, 1958, the patient resumed duty A year later she was on duty, fit, X-ray showed residual densities

Case 4.—A nurse, aged 18, was tuberculin-positive but had a clear chest X-ray on appointment in December, 1951 On Sept 20, 1955, isoniazid prophylaxis was started, and the drug was taken regularly for some months Thereafter isoniazid was taken irregularly, and none was taken while the patient was on leave from Jan. 5 to 25, 1959 On Feb 18, 1959, X-ray showed early infiltration and cavitation in the right upper zone. Cultural examination of sputum for *Myco tuberculosis* was positive. The organisms were insensitive to isoniazid in a concentration of 5 µg per ml. of medium, but sensitive to a concentration of 50 µg per ml On guineapig inoculation the organism caused lesions of spleen, liver, and lungs—virulence grading 18/18 The nurse was treated with 'Streptoneonizide' (an association of streptomycin and sodium methanesulphonate of isoniazid) 1 g daily for sixty days, then 1 g on alternate days, and P A S 12 g daily Sputum became negative in a month X-ray examination showed progressive improvement, and on Oct 20, 1959, the patient was discharged from hospital.

Case 5—A nurse, aged 21, was tuberculin-positive but had a clear chest X-ray on appointment on March 1, 1957, when isoniazid prophylaxis was instituted The patient was on leave from April 4 to 27, 1958 On May 18, 1959, X-ray showed considerable hilar node enlargement The diagnosis was not proved bacteriologically, but a presumptive diagnosis of tuberculosis was made in the absence of other positive findings The nurse has remained on duty while receiving treatment.

Case 6—A nurse, aged 33, was tuberculin-positive but had a clear chest X-ray on appointment in December, 1949 On Sept 20, 1955, isoniazid prophylaxis was started, but there is some doubt as to whether the drug was taken regularly On June 8, 1959, the patient went on leave, and on June 24, while still on leave, she was found to have a pleural effusion. The fluid contained *Myco tuberculosis* The organism was fully sensitive to isoniazid in vitro A guineapig inoculated with the pleural fluid showed tuberculous abscesses of inguinal and iliac nodes and one nodule in the spleen, but no lesion in liver or lungs virulence grading 8/18 The nurse was treated with streptomycin and isoniazid She resumed duty on Sept 14, 1959

Regularity of Isoniazid Prophylaxis

Nurses take isoniazid under supervision of the ward sisters They have not all taken it while on leave, and cases 4 and 6 suggested that they did not all take it when at work On Oct 2, 1959, this was investigated All nurse-aides on duty that day were assembled in four groups and were asked to complete a simple questionary about the regularity with which they were taking isoniazid The questionary was completed by 300 nurses—72 6% of the staff Nurses did not complete a form if they were off duty No identification was required on the forms It is felt that replies were honest and that an analysis gave a reliable picture of the problem

Isoniazid was taken regularly by 203 nurses (68%) of those who answered the questionary) The proportion of nurses taking isoniazid regularly rose from 56% of 131 nurses with four or more years of service to 87% of 60 nurses with less than a year's service The longer a nurse is on the staff, the greater is her opportunity for failing to take isoniazid, but this cumulative effect is not the sole factor That a nurse took isoniazid irregularly, but nevertheless took it on the day of the questionary or the day before, suggests that she was still attempting to take it If one accepts this inference, then of 58 nurses with four or more years' service who took isoniazid irregularly, 29 were still attempting to take it, whereas of 26 with less than three years' service, 19 were still attempting to take it A higher proportion of the nurses with long service had apparently given up the attempt

The old problem of self-administration of drugs has presented itself in another guise Constant reminders are necessary, particularly as the years of high incidence on the staff become more remote Since the time of the questionary, supervision and propaganda have been intensified

The commonest reason for not taking isoniazid, named by 37 nurses, was itch either alone or combined with other symptoms, 31 gave no reason, 10 admitted forgetfulness, 7 complained they became too fat Nurses were asked to report their individual difficulties and discuss them with a doctor Few came forward, presumably because their anonymity would be forfeit

Discussion

Tubercle bacilli recovered from 3 nurses (cases 3, 4, and 6) who developed tuberculosis after a period of isoniazid prophylaxis showed various degrees of isoniazid resistance in vitro and of virulence for guineapigs All these nurses have responded satisfactorily to treatment with isoniazid or its derivatives and streptomycin with or without P A S The outcome, judged by speed with which sputum was converted, the X-ray cleared, and the nurse returned to duty, compares favourably with the outcome of cases in which tuberculosis developed without previous isoniazid prophylaxis

Isoniazid prophylaxis is completely effective in babies (Dormer et al 1959) and calves (Dormer et al 1960) It is less certain in adults who can choose not to take it Nevertheless, it is worth while in a group of people where exposure to tuberculous infection is high

Summary

In September, 1955, prophylaxis with isoniazid 300 mg daily was initiated in a tuberculosis hospital among non-European nurse-aides These numbered about 600, of whom 16% were tuberculin-negative on appointment

In the next two years no case of tuberculosis was diagnosed in this group, in the third year only 1 case was diagnosed, but in the fourth year 3 cases were diagnosed

After four years, 32% of nurses were found to be taking isoniazid irregularly, and 68% regularly

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PERITONEAL DIALYSIS IN SALICYLATE INTOXICATION

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We report three cases of severe salicylate intoxication successfully treated by peritoneal dialysis Though this method has shown considerable experimental promise in dogs, it has not, as far as we know, been used before in man

Case-reports

Case 1 —A $2^1/_2$-year-old boy was admitted with a history of a mild attack of measles, which began four days before admission, and was complicated by progressive dyspnœa and drowsiness during the last twelve hours At the onset of dyspnœa the child was given penicillin, but the condition rapidly became worse When questioned the mother denied that she had given the child aspirin

He was gravely ill and had a fading morbilliform rash, a dry skin, and peripheral vascular collapse There were no clinical signs or radiographic evidence of pneumonia, but there was inspiratory effort and the respiratory rate was 32 per minute Temperature was 100°F and the pulse-rate 120 per minute A serum-ionogram showed sodium of 141 mEq per litre, potassium 3 mEq per litre, bicarbonate 10 8 mEq per litre, and chloride 110 mEq per litre The low serum-bicarbonate suggested the need for further investigation, and the serum-salicylate was found to be 38 2 mg per 100 ml The leucocyte-count was 26,100 per c mm (suggestive of dehydration), and the blood-glucose was 85 mg per 100 ml. No urine could be obtained by catheterisation

From previous clinical experience with these cases we realised that despite careful control of serum-electrolyte changes some patients still died There did not seem to be sufficient time to set up the artificial kidney, and peritoneal dialysis was therefore carried out at once

Two polyethylene tubes were inserted into the peritoneal cavity, one on each side, between the umbilicus and the superior iliac spine During the next four hours 4 litres of Hartman's solution * were dripped through the left catheter and collected from the right There was some seepage alongside the tubing, so that not all the fluid removed from the peritoneal cavity was collected

The breathing eased after the first hour and the child looked much better after the second There was rapid improvement following 5% dextrose given intravenously and recovery was then uninterrupted The dialysate contained 7 3 mg per 100 ml of salicylate Owing to the seepage the total amount removed could not be calculated exactly If all the fluid ran through, only 929 mg of salicylate were removed

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* Hartman's solution sodium 130 mEq potassium 4 0 mEq , calcium 2 7 mEq , chlorine 109 mEq , lactate 28 mEq

On further questioning the mother said she had given the child one 5-grain aspirin tablet every four hours for the last three days of his illness She believed that salicylates were quite harmless, and because of the initial time lapse, had not thought that this medication could be connected with her son's illness

Case 2.—A 5-month old girl was admitted in coma with rapid rhythmic dyspnœa, and chickenpox. The respiratory rate was 45 per minute, the temperature 103°F, pulse-rate 160 per minute

The child had dry skin and such severe dehydration that no blood could be obtained from the collapsed peripheral veins Coarse limb-twitching was noted, and a few scattered rales were heard in the chest. An X-ray of the chest was said to show "early inflammatory infiltration in the right upper and lower lobes and perhaps left upper lobe" This could not be confirmed clinically However, the white blood count by ear-prick was 17,000 per c mm, suggesting dehydration. A lumbar puncture was carried out to exclude encephalitis, the cerebrospinal fluid was normal Urine obtained by catheterisation contained salicylate.

The parents first denied giving any medication, but finally admitted giving half a 5-grain aspirin tablet three-hourly for the past three days They had not liked to admit home treatment

An electrocardiogram (E C G) showed some flattening of the T waves and from past experience a low serum-potassium was suspected. Peritoneal dialysis was carried out promptly using a rubber catheter to avoid seepage Bottles of lactated Hartman's solution, with 5% dextrose added to alternate bottles were used It was realised that the blood-glucose might be reduced too much if large quantities of dextrose-free fluids were given

During four and a half hours of dialysis, only 66 mg of salicylate was removed in 2 77 litres of dialysate, with concentrations ranging between 3 5 and 1 7 mg per 100 ml However the secretion of urine began shortly after the start of dialysis and concentrations of between 33 6 and 21 1 mg of salicylate per 100 ml persisted in urine for the next twenty-four hours As in the previous case the temperature fell abruptly during dialysis once sweating began.

Though no clinical change was noted in the initial thirty minutes of dialysis, there was a gradual return to full consciousness over the next three hours Dialysis was ended when respirations fell to normal, and recovery was uninterrupted.

Case 3 —A woman, aged 21, ate about sixty 5-grain aspirin tablets after a combat with an alcoholic husband. When admitted ten hours later she was irrational, breathing stertorously at 45 per minute, and apparently hysterical The skin was dry, temperature 101°F, pulse 100 per minute, and the serum-salicylate was 73 6 mg per 100 ml

No urine could be obtained by catheterisation and semi-coma steadily developed. A serum-ionogram showed sodium 148 mEq, potassium 2 8 mEq, bicarbonate 15 mEq, chloride 103 mEq An E C.G showed flattening of the T waves As the salicylate concentration was now at a lethal level it was decided to use peritoneal dialysis immediately and later to set up the artificial kidney if this still appeared necessary

As we now appreciated the importance of potassium depletion, we began with 1 litre of lactated Hartman's solution containing an extra 40 mEq of potassium

The patient became excited and complained of pain in the abdomen, but lapsed into semi-coma after a few minutes Thereafter 14 litres of Hartman's solution were used, with 5% dextrose in alternate litres, over the following three hours Concurrently an intravenous drip of 0 16 M sodium lactate was given for forty-eight hours to provide an excess of available base until the urine was free from salicylate There was no appreciable change for an hour, then breathing became less laboured, and sweating resumed with prompt remission of the pyrexia. After three hours full consciousness returned and respirations fell to 23 per minute. The total salicylate-content of the dialysate was 640 mg with concentrations up to 4 8 mg per 100 ml A copious diuresis began during dialysis and 3956 mg of salicylate was recovered in the urine over the next two days (see table)

BIOCHEMICAL SUMMARY

Serum electrolytes (mEq per litre)	Na	K	HCO₃	Cl	Salicylate (mg per 100 ml.)	Urine salicylate output (mg)
On admission	148	2 8	15	103	73 6	
8 hours after dialysis	133	2 0	21-5	103	55 7	2329
34 hours after dialysis	147	2 5	33 6	97 2	9 3	1487
58 hours after dialysis	150	4 2	27 3	112	0	140

Twelve hours after dialysis we became anxious because the patient was mildly drowsy and the blood-salicylate level was 55 7 mg per 100 ml. However, sweating was free, urinary output of salicylate was high and the respirations were 25 per minute Her improvement was rapid and our fears vanished during the day Convalescence was uneventful, apart from the appearance of occult blood in the fæces on the third day

Discussion

By chance we saw three cases of salicylate intoxication within a few weeks, and we were able to apply successively the lessons learnt from each In adults with uræmia caused by acute renal tubular necrosis we had used a Kolff artificial kidney with considerable success From previous experience of salicylate intoxication in children we realised that apparent correction of serum-electrolyte abnormalities, especially serious potassium deficiency, did not ensure survival We had therefore decided to use the artificial kidney, but faced with desperately ill small children and with the need for speed and simplicity we substituted peritoneal dialysis, using the modification described by Kolff (1955)

Later we discovered that a very careful study of treatment of experimental salicylate intoxication in dogs had been made by Etteldorf et al (1960) using intermittent peritoneal dialysis They showed that simple electrolyte solutions used as dialysates were relatively inefficient in removing salicylate from the body, when compared with those containing albumin Salicylate clearance increased in proportion to the concentration of albumin used We were unaware at the time that peritoneal dialysis had not been reported in human salicylate intoxication

Doolan et al. (1959) in a clinical evaluation of intermittent peritoneal lavage mentions incidentally that a significant amount of salicylate was present in the lavage fluid of one of their uræmic patients They comment that 'although no comparative studies have been performed, it seems unlikely that the rate of removal of aspirin, certain barbiturates, bromides or thiocyanate by intermittent peritoneal lavage would approach the rates which have been obtained with the artificial kidney"

Some biochemical lessons may be learnt from our experience In our three cases there was an evident and serious depletion of available base for enhancement of excretion of salicylate as conjugated glycuronide in the urine, and for the production of sweat. All patients showed severe dehydration with dry skin, absent perspiration (which returned shortly after treatment was started), and pyrexia (which dropped abruptly when base was made available in quantity and sweating began again) The oliguria was abruptly replaced by a diuresis which removed very large quantities of salicylate, in contrast to the relatively small amounts which appeared in the dialysing fluid All three cases showed either direct or presumptive evidence of a concurrent and dangerous potassium depletion This was most evident in case 3 (see table) where despite the provision of large amounts of potassium in the dialysing fluid, and in orange juice by mouth during recovery, the levels did not reach the normal range until more than two days later. Robin et al. (1959) have shown that this is a feature of salicylate intoxication and is probably due to direct salicylate effect on the excretion of potassium by the renal tubules.

On admission case 3 showed an apparently normal serum-sodium, but eight hours after dialysis despite the provision of considerable quantities of sodium-containing fluids the serum level was 133 mEq per litre. The total body-sodium is probably greatly depleted and this may be masked by the extent of the dehydration.

Almost every physician, who has encountered a number of these cases, stresses that " some patients poisoned by salicylates will die whatever is done " (*Lancet* 1960b). The complex actions of salicylates, which are not completely understood, appear to account for this. Segar and Holliday (1958) have pointed out these poorly understood and paradoxical effects of salicylates. For example, salicylate increases total body-heat production and yet is antipyretic in usual doses. However, the increased sweating which produces the antipyretic effect ends when the total available body-base is depleted and pyrexia then occurs, adding to the mimicry of acute infection, especially when accompanied by a leucocytosis induced by dehydration. The dehydration is then worsened by the dyspnœa. The cause of death in these patients is not clearly understood. Though it is known that hyperpnœa is one of the most valuable warning signs of salicylism, it appears to be produced by a number of factors acting in a set sequence. Initially there is direct stimulation of the respiratory centre, and the blood-pH shows a respiratory alkalosis, which probably enhances the renal excretion of base. This is followed by a metabolic acidosis, partly due to the acidity of aspirin and partly to an increase in unidentified lactate-like bodies, presumably derived from the over-exertion of the respiratory muscles. In small children ketone bodies from starvation play a minor part. Though intermittent 10% carbon dioxide and incomplete neuro-muscular block have both been ineffective, curarisation, and control of the respiratory rate by intermittent positive-pressure respiration have been life-saving by breaking the self-perpetuating metabolic acidosis (Freier et al. 1957).

Besides these important and severe blood-pH shifts there is a strong suspicion that some cases die from severe potassium loss (Robin et al. 1959).

It has been suggested that a plasma salicylate of 10 mg per 100 ml. is the critical level at which urgent treatment should be carried out (Rentsch et al. 1959). While this may be so it would still seem more important to provide plenty of available base for excretion of the salicylate in the urine.

We have not been able to lay down criteria for the use of this form of treatment, but have been guided by clinical experience, and have instituted dialysis in cases in which we felt that the patient would probably die in a matter of hours even although treated by intravenous 0·16 *M* molar lactate.

The clinical state of case 1 forbade any thought of a prolonged procedure such as replacement-transfusion. In any event, we now feel that the most effective way of allowing the patient to select his own electrolytes in quantity is by peritoneal dialysis.

It may well be a fallacy that gastric lavage is useless after the first few hours, for both acetyl and methyl salicylates are said " to remain in the stomach many hours before absorption and it is hardly ever too late to try to remove them " (*Lancet* 1960a). Garvie (1960) points out, however, that this may lead to pulmonary blockade by regurgitation and aspiration.

In addition, in a series of fifty-eight cases of salicylate poisoning reported by us elsewhere (Crichton and Elliott 1960), we have noted that the most serious were those due to therapeutic poisoning. The drug had been administered over a period of several days and often twenty-four hours or so had elapsed between the last dose and the time of diagnosis. This appears to be true in most other large series for example that of Segar and Holliday (1958).

In retrospect we had hoped to wash out the salicylates by dialysis, but we believe that we accomplished more by providing available base as a vehicle for enhancement of renal excretion of conjugated glycuronide.

Summary

Three cases of late salicylate intoxication are described in which peritoneal dialysis proved an effective form of treatment. This procedure was originally undertaken to remove salicylate directly, but was more beneficial in supplying large quantities of available base, including potassium, which had already been seriously depleted, presumably by earlier renal salicylate-excretion.

Though peritoneal dialysis in experimental salicylate intoxication of dogs has been studied, we are not aware of any reports of its clinical use in humans.

We are grateful to Dr. George Miller, Calgary Associate Clinic, for carrying out the surgery in the peritoneal dialyses.

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TREATMENT OF URTICARIA AND QUINCKE'S ŒDEMA WITH A SYNTHETIC ANTIMALARIAL DRUG: AMODIAQUINE

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This work originated in observations on a patient who used to have urticaria whenever she was exposed to sun light. One summer, when she was in Corsica, this did not happen. A possible reason was that, throughout her visit to the island, she was taking amodiaquine daily as a prophylactic against malaria.

Such an effect had been noted previously with amodiaquine (Sidi et al. 1959) and also with chloroquine (Artom 1959) and mepacrine (Cahn et al. 1951). That amodiaquine and other antimalarial drugs have therapeutic value in certain dermatoses—other than collagenoses—has been reported by the authors just cited and also by Bendi and Mirivet (1958), Gueorguieff and Bidekoff (1958), Meyer (1958), Meyer (1958), and Sidi et al. (1960) Some experimental work has demonstrated their anti-allergic action (Benda and Miravet 1958, Gueorguieff and Badekoff 1958)

The Present Series

These observations have led us to use amodiaquine regularly in the treatment of obstinate urticaria Of the 22 cases reported here, some were associated with Quincke's œdema The condition had lasted for periods ranging from six months to several years and had resisted anti-histamine therapy The patients were mostly young adults (age-range 20–60 years, average 35), and 13 were men

Amodiaquine Alone

In 12 cases amodiaquine was given alone, in doses of 200–400 mg daily during the first week and 200 or 100 mg daily during the second, third, and fourth Treatment was interrupted after four weeks, or maintained with low doses (100–200 mg weekly)

In 4 cases we had no response Here are two examples

Case 1 —Madame A , aged 35, had had Quincke's œdema and urticaria for five years, and amodiaquine (200 mg daily) brought no improvement Amœbiasis being suspected and proved, she was treated with 'Diphetarsone', and all symptoms disappeared.

Case 2 —Monsieur B , aged 27, had had urticaria with œdema and localised pruritus (Lewis' syndrome) for five years He got no benefit from amodiaquine either alone or with an anti-histamine Laboratory examinations showed an increase in β-lipoproteins and he improved after heparin therapy with a diet low in fats

The results have been excellent in 4 patients and good in 4 The urticaria was evoked in 2 by sunlight and in 2 by cold

Case 3 —Every winter for five years Monsieur C , a policeman, has had generalised urticaria and facial œdema when he is exposed to cold or when he washes with cold water Corticosteroid therapy and anti-histamine therapy has given no result Ten days after he began to take amodiaquine (200 mg daily for fifteen days) allergic manifestations disappeared The treatment was continued throughout the winter with 400 mg weekly

In 2 other patients allergy to food has been recognised Removal of the allergen from the diet has brought moderate improvement, but amodiaquine has done more good

Case 4 —Monsieur D aged 42 Daily attacks of urticaria and Quincke's œdema for one year Found allergic to wine, grape juice, crustacea, fish, and sea-molluscs (mussels, oysters), absorption of which results in intense urticaria Moreover, the patient is sensitised to the toothpaste he normally uses Removal of these allergens lessens the attacks, but they do not disappear After eight months' amodiaquine therapy (200 mg twice weekly) the attacks are less frequent and less intense Amodiaquine does not prevent the attack when an allergen (wine, for instance) is absorbed

Finally, in 2 other patients, men of fifty with urticaria of unknown origin, amodiaquine has given satisfactory results

Case 5 —Dr E , a surgeon, had had very intense urticaria for fifteen years Corticosteroids and antihistaminics had been ineffective Amodiaquine (200 mg daily) caused considerable improvement After three months' treatment, some attacks occur but they are very much lessened

Combined Treatment

In 10 other patients amodiaquine was given either with anti-histamines (7 cases) or with antibiotics (3 cases), both of which had proved ineffective by themselves We have had 4 failures no response in 3, and aggravation in 1

Of the 6 successful cases, the treatment had to be interrupted in 2 because of side-effects (nausea, vomiting, diarrhœa)

In 3 cases of intractable urticaria, antibiotics had been used on account of an infectious syndrome, pointed to by increase of erythrocyte-sedimentation time and of polymorphonuclear leucocytes (10,000 to 15,600) Amodiaquine with tetracycline and nystatin has given good results

Case 6 —Monsieur G , aged 22, had urticaria attacks with Quincke's œdema every winter The onset was at 6 months, immediately after anti-diphtheria vaccination Other remedies having failed, the patient was given tetracycline (500 mg daily) and nystatin (500,000 u daily) with amodiaquine (200 mg daily) After ten days the attacks disappeared After thirty days antibiotic therapy was interrupted but amodiaquine was maintained (100 mg daily) After sixty days all therapy was stopped and no urticaria attack has been observed since

(In 2 cases of asthma controlled by deltacortisone 10 mg daily, amodiaquine did not improve the quality of result or allow the dose of corticosteroid to be reduced)

Commentary

In 22 patients with intractable urticaria, amodiaquine was used alone (12 patients), or with anti-histaminics (7 patients), or with antibiotics (3 patients) It proved very effective in 14 cases—2 of sun urticaria, 2 of cold urticaria, 2 of digestive or food urticaria, 3 of infectious urticaria (amodiaquine associated with tetracycline), and 5 of undetermined urticaria

In 3, despite good results, amodiaquine treatment had to be discontinued because of digestive side-effects

Among the failures are a case of parasitic origin (chronic amœbiasis) and one of physical origin (mechanical irritation of skin) Consequently we do not think amodiaquine acts as blocking factor of the antigen Maybe, thanks to photo-protection, it inhibits formation of an autoantigen in the cases of sun urticaria But the action of amodiaquine is unknown, though from a strictly clinical point of view we can say that it seems to be anti-allergic Nor can we give any therapeutic schedule all we can say is that initial daily doses of 200 mg maintained for fifteen to thirty days seem to be satisfactory

The benefit, when there is any, appears during the first ten days of treatment It may continue after treatment stops, or sometimes a maintenance therapy with small doses (200 mg weekly) is required Undesirable side-effects are infrequent—in our series digestive disturbances in 2 patients, aggravation in 1, and asthenia in 2 The blood picture is unchanged However, as some incidents or accidents have been recorded (Meyer 1958, Artom 1959, Sidi et al 1960) it is necessary to be careful and, in cases of protracted therapy, to examine the blood every second month

Summary

Of 22 patients with urticaria, amodiaquine, in an average dose of 200 mg daily, gave good results in 14

This treatment may be associated with antihistaminics or with antibiotics

Side-effects are uncommon but should be borne in mind.

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CHROMOSOMAL TRISOMY ASSOCIATED WITH THE STURGE-WEBER SYNDROME

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A SURPRISINGLY large number of aneuploid conditions have been reported in man in association with particular congenital defects This applies to both the autosomes and the sex chromosomes The known cases of sex-chromosome aneuploidy have been recently summarised by Jacobs et al (1960) and Hayward (1960) These include monosomic and polysomic conditions All known autosomal aneuploids are trisomics

The first such occurrence was shown in conjunction with mongolism (Lejeune et al 1959, Jacobs et al 1959, Book et al 1959), more recently two additional cases have been described in children exhibiting multiple congenital defects (Edwards et al 1960, Patau et al 1960) Perhaps the most interesting report on autosomal trisomy is that of Fraccaro et al (1960) who have found a trisomic condition in the apparently normal father of a mongol child These four examples are all trisomic for different autosomes (see table) Our case provides a fifth distinct human male trisomic—in this instance associated with the Sturge-Weber syndrome

A SUMMARY OF HUMAN AUTOSOMAL TRISOMIC CONDITIONS

Clinical condition	Sex	Trisomic chromosome no	Reference
Mongolism	M & F	21	Lejeune et al (1959), Boök et al. (1959), Jacobs et al (1959)
Cerebral defect, simian creases, trigger thumbs, polydactyly, capillary hæmangiomata, *hare-lip, cleft palate,* apparent anophthalmia, heart defect	F	15	Patau et al (1960)
Peculiar facies, webbed neck, heart defect, neonatal hepatitis	F	17	Edwards et al. (1960)
Normal	M	19	Fraccaro et al. (1960)
Sturge-Weber syndrome	M	22	Present paper

Case-report

The patient, a boy aged 3 years 10 months, has lived in a residential nursery since the age of 14 months His mother died, aged 32, shortly after his birth His father and two siblings are healthy and there is no relevant family history Before his admission to the nursery he had frequent convulsions but since then phenobarbitone *has completely controlled them* Gross mental retardation was present then and little progress has occurred since

Present state —His general physical development is average (weight 35 lb (16 kg), height 38 in (97 cm) but his head circumference is only $18^3/_4$ in (48 cm) He shows gross mental retardation with hyperkinesis locomotor abilities are at 12-month level on the Griffiths scale, while other abilities (personal-social, hearing and speech, eye and hand, and performance) are at 6-month level A "port-wine" nævus covers the distribution of the ophthalmic and maxillary divisions of the right trigeminal nerve There is buphthalmos of the right eye (iridenclisis has been performed) His face is not suggestive of mongolism (fig 1) Mild left hemiparesis is present, the left calf is thinner than the right, the left arm is used less well than the right, and the left-arm reflexes are exaggerated.

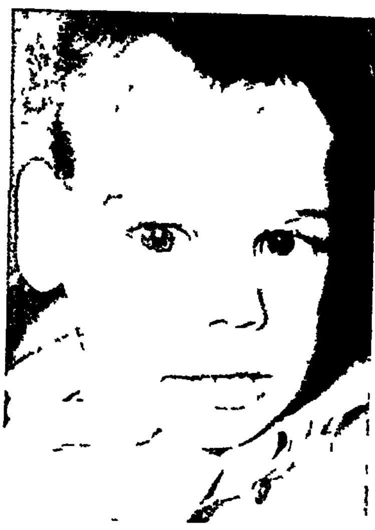

Fig 1—The patient, showing the extent of the facial nævus and the right buphthalmos

Investigations

X-ray of skull —The skull is smaller on the right There is extensive calcification in the right parieto-occipital region, with the gyral distribution typical of the Sturge-Weber syndrome (fig 2)

Electroencephalogram (after quinalbarbitone) —There is much less barbiturate fast activity over the right posterior region than over the left, and the slow sleep-activity is also less marked over the right parieto-occipital region than over the corresponding region on the left

X-ray of pelvis —The iliac index is 76° (the normal range for male babies is 68°–97° [Caffey and Ross 1956]) It is not known whether this finding has any significance after the 1st year of life, but, if the method is applicable later in life, the result *in this child is evidence against mongolism* (Dr Roy Astley)

X-ray of heart —Within normal limits

Analysis of prints of palms, soles, and fingers —Not suggestive of mongolism (Prof L S Penrose)

Cytological Observations

Iliac-marrow punctures were taken from both sides of the body and short-term cultures established These were subsequently treated by a modification of the standard method described by Ford et al. (1958) Details of this may be found in Hayward (1960)

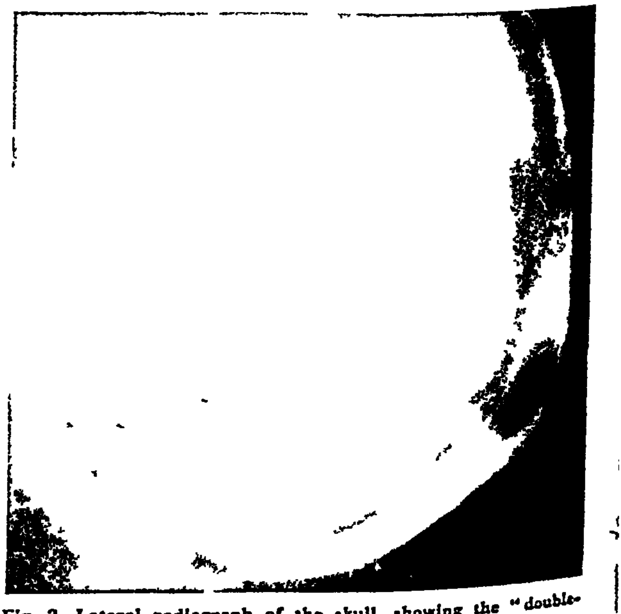

Fig 2—Lateral radiograph of the skull, showing the "double-contoured" gyral calcification typical of the syndrome.

Chromosome counts on unbroken well-spread cells were

Chromosome no	Number of cells counted	
	Right side	Left side
47	58	30
Polyploid	5	1
Total	63	31

Thirty-six cells were selected for detailed analysis and in these the sex-chromosome constitution was XY In all these cells six small acrocentric chromosomes were found as compared with five in the normal male (fig 3) Identification of the extra chromosome was difficult by size alone because of the similarity between pairs 21 and 22 It depended, therefore, on the presence or absence of satellites In none of the cells were there more than two of the small acrocentric chromosomes with satellites This means that the extra chromosome is probably no 22 (fig. 4), and not no 21, the trisomy of which is associated with mongolism (Lejeune et al 1959) This is supported by the clinical data, for none of the signs are those of mongolism.

Discussion

This is a typical case of the Sturge-Weber syndrome, with no other evident lesions It is at first sight surprising that an apparently localised, although gross, disorder should be associated with an additional autosomal chromosome, for with one exception the other patients in whom autosomal trisomy has been found have had widespread abnormalities involving several systems (see table) There is, however, pathological evidence that the abnormalities in this syndrome are not as localised as they appear to be Wohlwill and Yakovlev (1957) in a careful histological study of four cases, demonstrated angiomata in the lung, ovary, intestine, pituitary, choroid plexus, and the meninges, as well as in the skin of the face In addition, there were heterotopic groups of nerve-cells, scattered throughout the nervous system, apparently the result of failure of migration, and these groups of cells were unrelated to the angiomatous malformations The gasserian ganglion on the side of the facial nævus was abnormal in two cases There is, therefore, evidence of widespread dysplasia, affecting both ectodermal and mesodermal structures Nevertheless the syndrome does not exhibit the wide spectrum of abnormalities seen in mongolism, and in the cases of Edwards et al (1960) and Patau et al. (1960) It is of interest that the case described by Patau et al had multiple hæmangiomata, and it was this which prompted chromosome-study of our patient. Angiomatous malformations are associated with artificially induced aneuploids in salamanders (Fankhauser and Humphrey 1950)

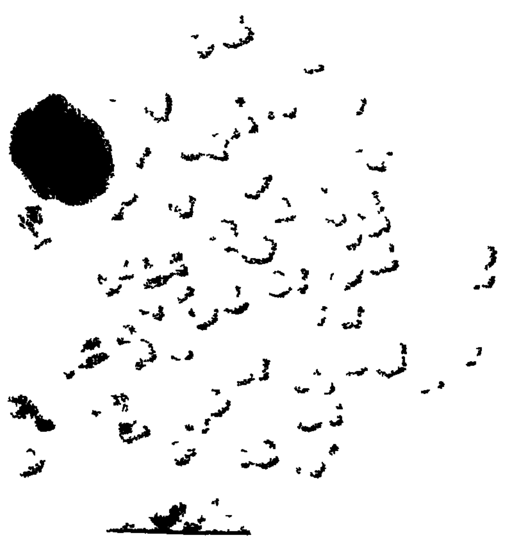

Fig 3—Mitotic metaphase in a bone-marrow cell. 2n = 47 (× 2500.)

There are few recorded instances of autosomal polysomy in animals Most of these occur in *Drosophila spp* thus in *D melanogaster*, individuals monosomic (haplo 4) and trisomic (triplo 4) for chromosome no 4 are hardly distinguishable from normal individuals Interestingly, however, flies tetrasomic for chromosome no 4 are inviable. Viable autosomal trisomics also occur in *D subobscura* (Philip et al 1944) All of these conditions are known only from flies bred in culture Callan (1941) has described a single individual, trisomic for the third largest autosome, in a wild population of *Mecostethus grossus*

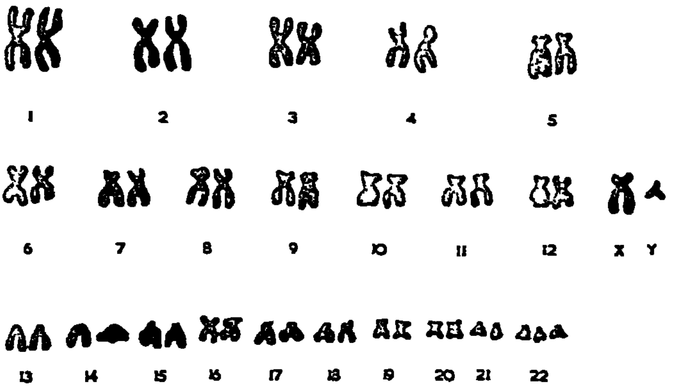

Fig 4—Chromosomes arranged in pairs showing the trisomy for no. 22.

As polysomic types are apparently rare, the recent discoveries of at least five human autosomal trisomics may seem surprising It would, however, be even more surprising if this reflected a genuine difference between man and other animals The more probable reason for this discrepancy is that in man studies have been confined to phenotypically abnormal specimens selected from large populations No comparable search has been made in other species Indeed it is possible that in species other than man these polysomic individuals would not survive to a stage where such an examination could be carried out.

In any organism trisomy results from chromosome non-disjunction This may occur at mitosis or meiosis

As far as the results of mitotic non-disjunction are concerned one can distinguish that type which occurs during early cleavage divisions of a developing embryo from that arising during the premeiotic mitosis in an adult body The first type should lead to somatic autosomal mosaicism the second to the production of aneuploid meiotic cells whose behaviour parallels that of cells in which non-disjunction occurs during meiosis In both cases the final result is the same—namely, the formation of unbalanced gametes The possible causal mechanisms which determine mitotic non-disjunction have recently been dealt with in detail elsewhere (Hayward 1960)

Non-disjunction at meiosis may occur during first or second division. Since meiosis II is effectively a haploid mitosis the mechanism and consequences of non-disjunction during this division are essentially mitotic in character and, presumably, similar causal mechanisms operate

Meiotic non-disjunction at the first division may depend upon three conditions the consequences of which are indistinguishable (1) failure of bivalent formation, (2) failure of the homologues of a normal bivalent to disjoin at first anaphase, and (3) irregular segregation of the components of a multivalent in a numerical hybrid or of a multiple configuration in an interchange hybrid (cf Darlington 1937)

(2) and (3) require no further consideration But failure of bivalent formation may arise in one of three ways (a) as a result of non-homology between the chromosome pair or pairs concerned, (b) as a result of asynapsis (i e, failure of pachytene pairing between completely homologous chromosomes), or (c) as a result of desynapsis (i e, failure of chiasma formation following successful pachytene pairing)

The first of these necessarily depends upon genic properties but the cause of both (b) and (c) may be either genotypic or environmental (cf Rees 1960), this is also true of both bivalent non-disjunction and irregular segregation at first anaphase

Which of these causal mechanisms determines the observed results of non-disjunction in our patient is not clear Nor as yet can we postulate a direct causal relationship between the trisomic condition found and the distinctive phenotype of the Sturge-Weber syndrome This uncertainty is by no means confined to our case, the same consideration may be applied without qualification to the trisomics described by Edwards et al (1960) and Patau et al (1960) In both of these cases it has still to be unambiguously demonstrated that autosomal trisomy is the cause rather than an accompanying phenotypic effect expressed at the nuclear level, or a chance association of events. Indeed only in mongolism is it even possible to suggest a relationship between cause and effect, since no normal complement has yet been found in a mongol, it may be reasonably accepted that the abnormal chromosome condition is causal in the production of the defective phenotype This whole problem of interpretation in such cases is made more difficult by the discovery of a clinically normal male, trisomic for the 19th autosome, by Fraccaro et al (1960) Only further studies can clarify the situation in respect of autosomal polysomy in man

Summary

A case of autosomal trisomy associated with the Sturge-Weber syndrome is described The extra chromosome is cytomorphologically comparable to the five smallest acrocentric chromosomes found in normal males Reasons are given for its probable identification as no 22

The implications of the trisomy and its relation to the abnormal phenotype are discussed

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CHRONIC Q FEVER WITH MITRAL-VALVE ENDOCARDITIS

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Q FEVER, like the other rickettsial diseases, may be met with in two forms.

The typical illness is an acute systemic infection of abrupt onset with pyrexia, muscle pains, and headache, often associated with pneumonitis In most acute infections, however, symptoms are probably either absent or so mild that the nature of the disease is unrecognised The frequency of these subclinical infections can be estimated only by serological surveys of the normal population Evans (1956), for example, showed that although about 4% of blood donors in South Wales had specific complement-fixing antibodies for Q fever, only 15 of 2482 consecutive cases of non-bacterial pneumonia were caused by *Rickettsia burneti*

Rarely, Q fever may take a more chronic course Little is known of the clinical manifestations of this chronic form, but two cases of endocarditis directly due to *R burneti* have been described recently (Evans et al. 1959, Robson and Shimmin 1959, Andrews and Marmion 1959) In both cases the patients were shown at necropsy to have grossly damaged aortic valves, rickettsial bodies were found in the lesions, and *R burneti* was isolated from the aortic valves and the spleen. These findings, in the presence of antibody to both antigenic phases of *R. burneti*, were considered good evidence that the illness was a form of Q fever In neither case, however, could it be shown that there was pre-existing valvular damage

This paper describes a patient who presented the features of chronic Q-fever endocarditis superimposed on rheumatic mitral stenosis

Case-record

The patient, aged 33, a locomotive driver, was first seen in 1951 at the Royal Gwent Hospital, Newport, complaining of slight effort dyspnoea He had had rheumatic fever four years earlier The diagnosis of pure mitral stenosis of moderate severity was made In July, 1955, because of increased effort dyspnoea, he was referred to the Chepstow Chest Unit, for mitral valvotomy The clinical signs were then those of tight mitral stenosis with a pliant valve, and sinus rhythm A soft, early diastolic murmur was audible at the pulmonary area At operation on Nov 9, 1955, the valve just admitted the tip of the index finger The valve was partially split with the finger Considerable improvement in effort tolerance followed the operation, and he was seen as an outpatient at regular intervals

He remained well until April, 1957, apart from three episodes of "influenza" in January, February, and March, 1957 These lasted two to three weeks and were characterised by moderate pyrexia, malaise, and muscle pains In April, 1957, after palpitation (due to the onset of atrial fibrillation), and pain in the right hypochondrium, he was admitted to the Royal Gwent Hospital There was no pyrexia The liver was two fingerbreadths enlarged but the spleen was not felt

In November, 1957, he had a further episode of "influenza" and thrombosis of the deep veins of the left calf developed

In September, 1958, he was readmitted with a history of recent "influenza", followed by pain in the left loin and the hypochondrium There was slight pyrexia at first The liver was hardly palpable but the spleen was now slightly enlarged. The left renal area was tender On discharge twelve days later he was apyrexial

In November, 1958, he was again admitted because of deterioration in general health. Finger-clubbing was noted. Antistreptolysin O (A S O) titre was 500 units (one week later 200 units)

Treatment with aspirin gr 15 three times daily was begun as the presence of rheumatic activity was suspected. Shortly after he complained of considerable pain and tenderness in the left hamstrings and left middle finger

In February, 1959, he again had "influenza"

In June, 1959, he was readmitted because of increased effort dyspnœa and pain in the right hypochondrium He complained of recent leg pains and occasional attacks of nocturnal dyspnœa He had lost 14 lb in weight during the previous six months Examination revealed atrial fibrillation and considerable mitral stenosis The liver was enlarged by three fingerbreadths The spleen was easily palpable and tender A mild, intermittent pyrexia was present

He was transferred to Sully Hospital on July 9, 1959 His general condition was poor and he was thin and orthopnœic The fingers were grossly clubbed, and there was erythema of the palms and cuticles The extremities were warm There were no petechiæ, Osler's nodes, or rash The pulse-volume was small The jugular venous-pressure was −6 cm at 45° Blood-pressure 110/75 mm Hg The heart was moderately enlarged and the right ventricle was prominent The left ventricle was not palpable The liver and spleen were enlarged by seven and five fingerbreadths respectively, and were moderately tender and firm

A chest radiograph showed enlargement of right ventricle and left atrium The main pulmonary artery was larger than in 1955, and the lung fields showed the pattern of combined venous and arterial hypertension The electrocardiogram showed atrial fibrillation, right ventricular hypertrophy, and digitalis effect Temperatures ranged from 98 to 100°F

Investigations

Urine—trace of albumin No abnormal deposits Hæmoglobin 80% (11 7 g), white blood count (W B C) 7000 per c.mm (neutrophils 65%, lymphocytes 20%, monocytes 5%), erythrocyte sedimentation-rate (E S R) 27 mm in one hour (Westergren) (July 10), 29 mm (Oct 12) Electrolytes normal Thymol-turbidity 2 5 units Künkel 6 units Alkaline serum-phosphatase 21 King-Armstrong units, serum glutamic oxyacetic transaminase 8 units Bilirubin 0 5 mg Plasma-protein 6 g per 100 ml (albumin/globulin ratio 3 3) Electrophoretic pattern normal Blood-urea 45 mg per 100 ml , A S O titre 200 units No occult blood in stools Venous blood-cultures (6) negative, after prolonged incubation Arterial blood-cultures (3) negative.

Virus Studies

Q fever	*July 29*	*Sept 9*	*Sept 14*
Phase 1	1/256	1 128	1 128
Phase 2	1,256	1 128	1 128
Murine typhus	<1 8	<1 8	<1 8

Complement-fixation tests for influenza A, B, and C, psittacosis-lymphogranuloma, adenovirus, lymphocytic choriomeningitis, tests for *Streptococcus MG*, and cold agglutinins were negative

These findings suggested a diagnosis of chronic Q fever

When questioned, the patient denied drinking raw milk, and said he had had no contact with domestic ruminants

Progress and Treatment

Initially he was treated with strict low-sodium diet, hydrochlorothiazide, digoxin, and oral iron His jugular venous-pressure fell to normal and he was able to sleep lying fairly flat On July 26 he developed slight hæmoptysis, severe right pleuritic pain, and an extensive pleural rub Anticoagulation with phenindione ('Dindevan ') was started on the assumption that he had pulmonary infarction. He continued to have intermittent hepatic pain and at times tenderness was sufficient to suggest hepatic infarction On Aug 25, hæmoglobin had fallen to 60% (9 65 g), W B C 8800 per c.mm., platelets 110,000 per c mm. The red cells were slightly hypochromic The sternal marrow was hyperplastic and normoblastic with many macronormoblasts The thymol-turbidity and Künkel tests gave a value of 10 and 20 units, respectively

By Sept 18 the hæmoglobin had fallen to 48% (7 0 g), hæmatocrit value 24%, mean corpuscular hæmoglobin concentration 29%, reticulocytes 3% The orthopnœa had grown worse, and so concentrated cells from two pints of blood were transfused On Sept 15, after consideration of the final report of the virus studies, it was decided to start treatment with oxytetracycline (terramycin), 2 g daily for seven days, followed by erythromycin, and chloramphenicol, 2 g of each daily The slight pyrexia soon abated and did not recur His general condition improved greatly and the hæmoglobin rose rapidly to 88% (12 9 g) The liver and the spleen decreased in size and became less tender Inoculation of blood and urine into guineapigs gave negative results

A second mitral valvotomy was performed on Oct 29, the administration of erythromycin and chloramphenicol having been continued until then The pericardium was closely adherent The pulmonary artery was large and tense, and the aorta small The left atrium was moderately enlarged with a small appendage The mitral valve again barely admitted the fingertip The cusps were fibrotic without palpable regurgitation or calcification Entry to the left atrium was difficult and after three attempts a moderate split of the mitral valve was achieved with a Dubost dilator Several hours after the operation, he developed cardiorespiratory failure which failed to respond to the usual measures

Necropsy

The air passages contained a small amount of viscid mucus Both lungs were congested, œdematous, brownish in colour, and indurated There was a small wedge-shaped scar on the diaphragmatic surface of the right lower lobe and a similar scar subpleurally on the left lower lobe

The heart weighed 500 g The left atrium was hypertrophied and dilated, as was the right atrium The right ventricle was considerably hypertrophied. The mitral valve was stenotic and slightly incompetent, and the condition had been only partially relieved by valvotomy There was a traumatic septal defect consisting of a tear, about 1 5 cm long, in the interatrial septum There was a roughened area on the posterior cusp of the mitral valve with some brownish vegetations

The liver was congested. The spleen was enlarged, weighing 700 g , firm in consistence and dark red in colour

There was an old healed infarct in the left kidney

Histology and Bacteriology

The mitral valve was thickened and fibrosed, and in one area there was an organising thrombus on the surface beneath this there was a collection of inflammatory cells consisting of neutrophils, lymphocytes, and mononuclears A preparation of this area, stained by Macchiavello's method showed rickettsia-like bodies

The smaller branches of the pulmonary artery showed the changes of reactive pulmonary hypertension

Suspensions of the mitral-valve vegetations, spleen, liver, and kidney were inoculated into guineapigs previously shown to be free from antibodies for *R burneti* Two animals were used for each specimen Six weeks after inoculation the animals were bled and their serum tested by complement-fixation Both guineapigs inoculated with mitral-valve suspension had antibody titres of 1/256 for *R burneti*, whereas the others were negative These tests were repeated with identical results

Discussion

Although Marmion et al (1953) suggested that chronic Q fever might occur when the specific infection was superimposed on pre-existing heart damage, in neither of the two previous cases of proved Q-fever endocarditis was there good evidence of this Our patient had been treated for rheumatic fever twelve years before we saw him and had undergone a valvotomy for mitral stenosis eight years later His infection with Q fever apparently occurred about two years after this

Any patient with the symptoms of infective endocarditis but with negative blood-cultures should have serum tests for Q fever in addition to guineapig inoculation tests of blood and urine If cases of infective endocarditis with negative blood-culture are indeed due to chronic Q fever, the commonly advised treatment with penicillin and streptomycin will not prove effective *R burneti*, however, is usually sensitive to oxytetracycline and the other broad-spectrum antibiotics, and these are better used in combination On present evidence, the prognosis in these cases is grave

Summary

A patient in whom rheumatic mitral stenosis was diagnosed in 1951 had the first of a series of episodes of " influenza " in February, 1957 Features suggestive of infective endocarditis were first noted in September, 1958 Blood-cultures and other investigations were negative, but in September, 1959, serological evidence of chronic Q fever was obtained

A good therapeutic response followed antibiotic therapy with the broad-spectrum antibiotics

The patient died after mitral valvotomy At necropsy, small vegetations were present on the posterior cusp of the mitral valve Guineapig inoculation of suspensions of the vegetations produced high antibody titres for *R burneti*, and rickettsia-like organisms were seen in sections of the vegetations

Chronic Q fever should be suspected in patients with the clinical picture of infective endocarditis and negative blood-cultures The organism is not sensitive to penicillin or streptomycin

We wish to thank Dr E Graham Jones, Dr L R West, and Mr T H L Rosser for permission to describe this case Dr R M E Seal performed the necropsy and gave much helpful advice

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PIGMENTED NÆVUS OF NAIL

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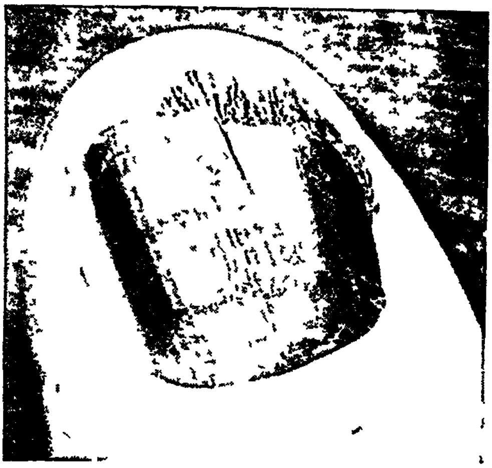
ALTHOUGH the clinical picture of the melanotic whitlow is well known to surgeons and dermatologists, a solitary pigmented (linear) stripe of the fingernail caused by an underlying pigmented nævus may give rise to diagnostic difficulties Because early diagnosis followed by appropriate surgery carries with it a fairly good prognosis, it is important that this comparatively rare condition should be recognised

Clinical History

The patient, a Hungarian woman aged 39, was seen in the dermatological department of University College Hospital in October, 1959, with a four-year history of discoloration of her right thumb-nail This had begun as a pigmented longitudinal stripe which had slowly extended laterally to involve the whole nail except one narrow well-defined segment (see figure) Four months earlier, the nail had cracked longitudinally without any preceding trauma The whole process had been completely painless, there was no associated inflammation, and the patient asked for advice about treatment because the ragged fissured nail caught in her clothing



Pigmented nævus of nail

Her general health was excellent and she had had no serious illnesses or operations

The right thumbnail was uniformly black except for a segment of normal-coloured nail extending the length of the nail-plate It was fissured longitudinally and under the free edge of the nail there was a small amount of friable pigmented material There was no associated inflammation, lymphadenopathy, or hepatomegaly, and there were no other pigmented lesions

Investigations

Nail-clippings were partially macerated in 20% solution of potassium hydroxide No fungus could be found on microscopic examination Abundant dark pigment was seen, both intracellularly and lying free, in the nail The pigment did not give a positive reaction for iron but was partially decolourised by soaking in hydrogen peroxide, thus indicating that it was melanin

The probable diagnosis of a junctional pigmented nævus of the nail-bed was made, and under local anæsthesia the nail was avulsed This revealed a deeply pigmented lesion, and a portion from the nail matrix was excised for histological examination

The histological appearance was that of a junctional nævus with junctional activity and abundant pigment lying in the dermis The pigment again proved to be melanin

Because of the site, and the recent break in the continuity of the nail-plate which indicated either an extension of the nævus or a developing malignant change, it was thought advisable to amputate the terminal phalanx This was done in December, 1959, and healing was uneventful

Discussion

The first reference to this condition was made in 1917 by Montgomery who reported a case of a white man, aged 36, who developed a pigmented stripe in his thumbnail The stripe was first noted one month after superficial X-ray treatment for eczema of his hands Although there was no histological evidence to support the diagnosis, Montgomery stated that the most reasonable explanation for the phenomenon was that there was a pigmented nævus, situated in the nail groove, producing pigment in the newly formed nail

Templeton in 1926 reported a similar case in a Negro woman, aged 28, affecting the left fourth finger and although the presumptive diagnosis of a pigmented nævus was made, there was again no histological confirmation

Engman et al (1931) reported a case of a melanotic whitlow which had begun four years previously, as a wide streak extending the length of the nail Similar cases of malignant melanomata have also been recorded in papers by Wormack (1927), and Pack and Adair (1939) The latter stated that a pigmented spot under the nail may remain quiescent for a long time as pigmented nævi often do in other parts of the body Pigmentation had been noted for periods of from two to ten years They regarded a nævus as being clinically malignant when it broke through the nail.

Pardo-Castello (1941) recognised the longitudinal pigmented bands in nails as deposits of melanin probably secondary to the presence of pigmented nævi in the nail matrix which might have been there since birth The natural history of the condition was not studied nor was histological evidence provided

Noble et al (1952) recorded a case of a pigmented stripe, which had been present for four years, in the fifth left fingernail of a 24-year-old white man The terminal phalanx of the affected finger was amputated and three years later there was no evidence of local recurrence or of metastasis The histological diagnosis was that of a benign junctional nævus of the nail matrix

Unfortunately, few patients come for advice and treatment at the stage when nothing more than a pigmented stripe or spot appears on the nail-plate, and they would probably be reluctant to part with a useful portion of a digit for a seemingly trivial complaint Amputation, however, does seem to offer a good chance of a cure for a condition which, at a later stage, carries a notoriously bad prognosis In Negroes, longitudinal bands of melanin pigmentation affecting one or more nails are more common The pigment is melanin arising from normally functioning melanocytes in the matrix, and the condition, being completely benign, requires no treatment (Pillsbury et al 1956)

I wish to thank Dr P J Hare for permission to publish this case, Dr J Smith, and Dr Arthur Jarrett for the histological reports, and Mr David Bailey for carrying out the avulsion and the amputation

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Preliminary Communication

X-RAY-INDUCED CHROMOSOME DAMAGE IN MAN

EVIDENCE that X rays and other types of nuclear and allied radiation cause chromosome damage has been forthcoming for many years, and has accumulated from the study of a variety of plant and animal tissues [1] From these studies it had been generally assumed that the production of chromosome damage in man was an important mechanism in the establishment of the acute clinical effects of radiation exposure, and possibly also was the cause of such delayed effects as the induction of leukæmia.[2]

TABLE I—CHROMOSOME-COUNT DISTRIBUTIONS 6 NORMAL SUBJECTS

—	Chromosome counts							Total cells counted
	<44	44	45	46	47	48	>48	
Male			2	32				34
"		1	4	29	2			36
"			1	30				31
Female			4	39				13
"				30				30
"			1	30				31
Totals		1	12	190	2			205
Percentage		0 5	5 8	92 7	1 0			100 00

As far as direct observations on human tissues are concerned, Fliedner et al.,[3] using simple squash preparations of bone-marrow, noted evidence of chromosome "stickiness", clumping of chromosomes, and anaphase bridge-formation in a number of persons accidentally exposed to a mixed neutron/gamma-ray beam Bender,[4] Puck et al,[5] and Chu and Giles [6] have studied the effects of radiation exposure in vitro on human tissue-culture preparations Only recently, however, has it become possible to undertake serial studies of chromosome changes in the directly irradiated human being This present communication reports the results of such studies in two patients given X-ray treatment for ankylosing spondylitis

TECHNICAL CONSIDERATIONS AND RESULTS

The chromosome preparations were made from blood-cultures using an adaptation of the technique of Hungerford et al [7] the final spreading of the chromosomes being achieved by drying in air With this technique a count of the chromosomes in 205 cells from six normal subjects showed 190 cells (92 7%) to have 46 chromosomes (table I) This proportion of modal cells did not differ significantly from that in a study of 489 cells from sixteen patients suspected of having chromosome abnormalities but who were found to have apparently normal karyotypes (table II) 449 cells had a count of 46 chromosomes (91 8%) and variations from this modal number are attributed mainly to artefacts arising during preparation Court-Brown et al [8] have discussed the causes of variation from the modal number in chromosome counts made on bone-marrow preparations The improvement in the quality of the preparations, which has followed the introduction of the present technique, is evident from the finding that of 1602 cells from bone-marrow preparations 85% only had a count of 46 chromosomes A comparison of the count distributions in the pre-exposure blood-samples from the two patients cited

TABLE II—CHROMOSOME-COUNT DISTRIBUTIONS 16 PATIENTS WITH NORMAL KARYOTYPES

Sex	Diagnosis	Chromosome counts							Total cells counted
		<44	44	45	46	47	48	>48	
M	Arthrogryposis		1		29				30
M	Anophthalmia				31	2			33
F	Spastic diplegia			1	29				30
M	Pelger-Huet anomaly			3	28				31
F	Pelger-Huet anomaly			2	27	1			30
M	Hydrocephalus		1	3	26	1			31
M	Infertility		1	1	29				31
M	Infertility			3	28				31
M	Infertility			1	29				30
F	Primary amenorrhœa				27	1			28
F	Testicular feminisation			4	26	1			31
M	? Marfan s syndrome		1	1	26	1	1		30
M	? Fanconi s anæmia			1	30				31
M	? Mongolism			2	29	1			32
F	Primary amenorrhœa			1	28	1			30
F	Primary amenorrhœa			2	27	1			30
	Totals		4	25	449	10	1		489
	Percentage		0 9	5 1	91 8	2·0	0 2		100 0

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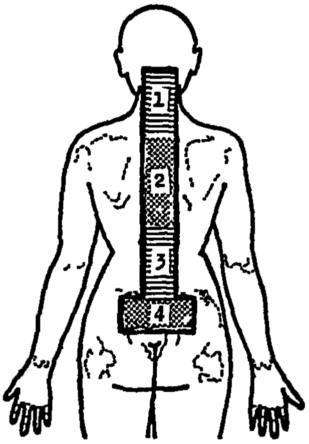

Fig 1A

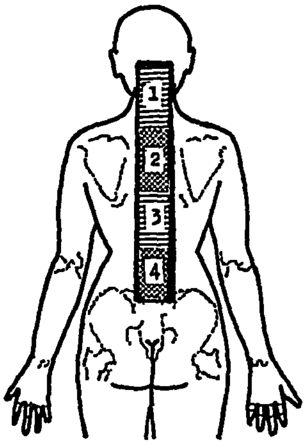

Fig 1B

Fig 1A—Arrangement of X-ray fields and physical characteristics of X-ray beam (Patient A)

Fig 1B—Arrangement of X-ray fields and physical characteristics of X-ray beam (Patient B)

kV 250, mA 15, half-value layer 2 7 mm Cu, focus-skin distance 50 cm

	Field size (cm)		*Dose-rate (rads per min)*	
	A	B	A	B
1	15×10	20×7 5	67 5	66 8
2	20× 7 5	15×7 5	66 8	67 1
3	20× 7 5	15×7 5	66 8	67 1
4	15× 7 5	15×7 5	67 1	67 1

below with those in tables I and II, shows these distributions to be within the normal range of values for the present technique

The two male patients studied were given X-ray treatment for ankylosing spondylitis The first patient (A) received treatment to the whole length of his spine and to his sacroiliac joints between July 18 and July 29—a total skin-dose of 1500 rads being given in 10 equal fractions In the second patient (B), the effect of a single dose of X-rays, 250 rads to the skin over the spinal column alone given on Aug 10, was studied over a period of ten days by serial blood-cultures The field arrangements and the physical characteristics of the X-ray beam are shown for both patients in figs 1A and 1B

Cells were selected for counting provided that all the small chromosomes (nos 13 to 22 and the Y chromosome in the Denver classification) were easily identifiable, and in every selected cell these were analysed It will be seen from tables III and IV that polyploid cells were noted in most of the preparations These polyploid cells are not included in the chromosome-counts as they can be recognised without a precise count being made For purposes of comparison, however, an approximate measure of the frequency of polyploids is indicated by the fact that only two were noted during the study of the 694 cells listed in tables I and II The last technical point to be mentioned is that one of the common effects of radiation is the production of chromosome fragments, and in counting the chromosomes we have adopted the convention of scoring a fragment as a whole chromosome Thus, a cell with 46 chromosomes and a fragment would be recorded as having 47 chromosomes

The effect of X-ray exposure on the chromosome constitution of each patient is shown in table III (patient A) and in table IV (patient B)

DISCUSSION

The data from the first patient show clearly that a heavy, accumulated dose of X rays produces considerable chromosome damage This is shown by significant changes in the count distribution and by a considerable increase in the numbers of cells carrying chromosomes with structural abnormalities These latter are of many types and no attempt will be made to describe them in this preliminary communication, it is worth noting, however, that chromosome fragments are common and that complex abnormalities such as ring chromosomes and dicentrics are seen (figs 2 and 3)

The data from the second patient are more informative A single X-ray exposure was given on Aug 10 and twenty-four hours later two significant changes had occurred By then the percentage of cells with 46 chromosomes had fallen from 93 to 72, and that of cells with structurally abnormal chromosomes had risen from 1 to 22 The fall in the modal cells was due to a remarkable increase in the number of cells with 47 chromosomes, which rose from 1% to 21% During the five days from Aug 12 until Aug 17 six blood-cultures were set up but only four were successful, and two of them—Aug 12 and Aug 13—were of poor quality This partial failure may be associated with some effect of irradiation The unusually low count of modal cells was still present three days after exposure, and on this day the percentage of cells with chromosome structural abnormalities reached a maximum

TABLE III—CHROMOSOME DATA—PATIENT A

—	Chromosome counts							Total cells counted	Modal cells (%)	Cells with chromosome structural abnormalities (%)		Polyploids
	<44	44	45	46	47	48	>48			Modal cells	All cells	
July 18 (pre-exposure)	1		3	44	2			50	88	0	2	0
July 22	1	1	7	33	6	2		50	66	18	40	0
Aug 2			7	37	2	1	3	50	74	19	34	11
Aug 12	1		5	34	7	1	2	50	68	9	32	7
Aug 18			5	43	1	1		50	86	16	18	3

The changes in the proportion of modal and non-modal cells found on July 22, Aug 2, and Aug 12 by comparison with the proportion in the control blood of July 18 are highly significant The values of χ^2 and P (n=1) are respectively 22 92 and <0 001, 9 29 and <0 01, and 18 96 and <0 001

TABLE IV—CHROMOSOME DATA—PATIENT B

—	Chromosome counts							Total cells counted	Modal cells (%)	Cells with chromosome structural abnormalities (%)		Polyploids
	<44	44	45	46	47	48	>48			Modal cells	All cells	
Aug 10 (pre-exposure)			5	93	1		1	100	93	0	1	1
Aug 11	1	1	4	72	21	1		100	72	7	22	11
Aug 12	1		3	27	4			35	77	18	23	1
Aug 13			1	19	2	3	2	27	70	27	41	0
Aug 15			2	90	6	1	1	100	90	11	16	3
Aug 17			3	93	2	1	1	100	93	6	11	0
Aug 19		2	3	89	4		2	100	89	4	10	6
Aug 21			1	90	9			100	90	2	9	8

The changes in the proportion of modal and non modal cells found on Aug 11, Aug 12, and Aug 13 by comparison with the proportion in the control blood of Aug 10, 1960, are highly significant The values of γ^2 and P (n=1) are respectively 67 74 and <0 001, 13 52 and <0 001, and 21 24 and<0 001

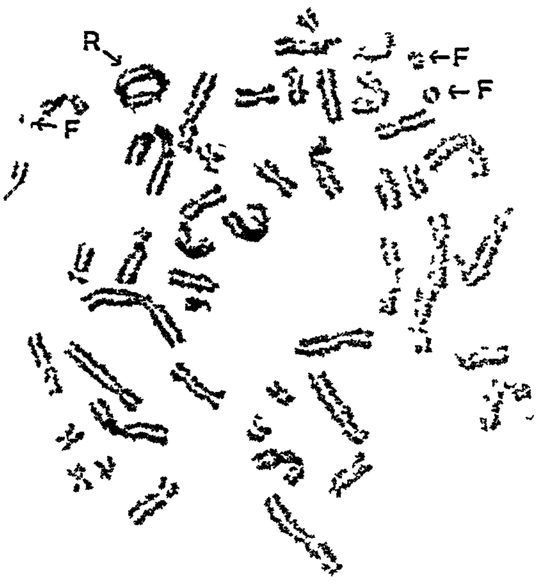

Fig 2—Cell from patient A, with 50 chromosomes, showing ring chromosome (R) and fragments (F)

By the fifth day, however, the percentage of modal cells had returned to within normal limits, and remained so for the rest of the period of observation The fifth day also marked a decline in the number of cells with structural abnormalities, but even on the last two days of observation these were present in 9 to 10% of the cells

In both patients unusual numbers of polyploid cells were seen. Perhaps the most striking increase was that occurring twenty-four hours after the X-ray exposure of the second patient. At this time 11 polyploids were noted during the finding and counting of 100 cells with diploid or near-diploid numbers

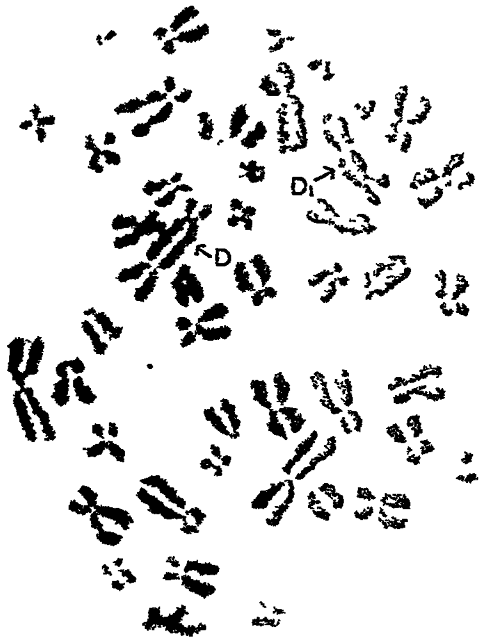

Fig. 3—Cell from patient A, with 46 chromosomes, showing one definite dicentric chromosome (D) and a second possible dicentric (D_1).

Findings resembling these have been noted by us in cases of chronic myeloid leukæmia after X-ray treatment. These will be discussed in a later communication.

In conclusion, the data indicate, as might be expected, that X rays readily produce chromosome damage which can be detected in cultures of human blood-cells. Much more work will be necessary to achieve a fuller understanding of the pattern of the changes, particularly the effect of varying such physical parameters as the total dose and the dose-rate. What we have learnt about the extent of the damage produced by a single dose of 250 rads, limited to the skin over the spinal column, gives grounds for hoping that the relationship between radiation dose and the extent of chromosome damage in man may be evaluated by direct observation over a wide range of doses

We are indebted to Prof R. McWhirter and his staff for access to patients under their care, and to Miss M. Brunton and Miss G Woodcock for technical assistance.

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New Inventions

A DEVICE FOR CONTROLLING THE FLOW OF PARENTERAL INFUSIONS

A SMALL, reliable, and inexpensive device has been developed for monitoring the flow of parenterally administered solutions It alerts the attention of the nurses and also automatically stops the flow when the predetermined volume has passed.

Fig 1 is a diagram of the apparatus, and fig 2 represents

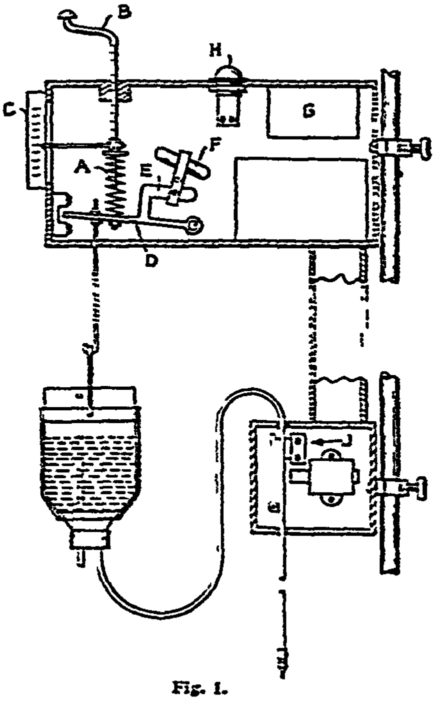

Fig. 1.

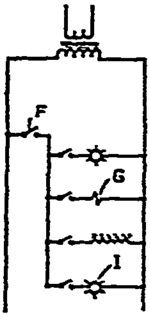

Fig. 2.

the electrical circuits. The tension on the spring (A) is set by a crank (B) which points on a scale (C) calibrated in units of 50 ml. of solution. As the preset volume is consumed, the infusion bottle loses weight and rises. This movement is translated by levers (D and E) into the closing of a mercury switch (F). When the switch closes, the triple-alarm system and the automatic flow cut-off are activated. The alarm comprises a ringing bell (G) and a red flashing light (H) at the bedside, and another flashing light (I) at the nurses' station. The automatic flow cut-off attachment (J) is an electromagnet of the hinge-clapper or solenoid type, which pinches off the plastic tubing through which infusion flows. This cut-off device and the alarms are wired in parallel, each with its own switch, to provide the greatest versatility.

If every 50–100 ml. of infused solution is thus monitored, acute pulmonary œdema, due to inadvertent acceleration of the speed of infusion in patients with compromised cardiac reserve, would be decreased. If the apparatus is set at some point before complete emptying of the infusion bottle, the danger of air-embolism due to positive-pressure fluid administration (e.g., during cardiac catheterisation) would be slight. By alerting attendants before complete consumption of the solution, the device would diminish the frequency of repeated venepunctures due to clotted needles—a constant source of irritation to patients and house-staff alike—and would obviate the necessity for "cut-downs" in patients with inaccessible veins.

Yonkers, New York,
U.S.A.

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M.D.
MURRAY A. EDIS
B.M.E.

A CONTROL UNIT FOR SUCTION WITH REPEATED RELEASE

HOWEVER elaborate or expensive surgical suction apparatus may be, it is useless if the suction tube becomes blocked. This may happen when the volume to be aspirated is small, as in infants, because tissue surfaces are drawn in by the negative pressure over the open end of the tube. If the suction is constant this fault is unlikely to clear itself.

Repeated manual aspiration by a trained nurse is one solution to the problem, but this is expensive in terms of skilled time. In the United States pumps with an intermittent suction action are widely adopted, and, although these still require supervision, they do save nursing time.

Better results can be expected (except in the pleural cavity) if the suction is briefly and repeatedly alternated with atmospheric pressure. The apparatus here described has been designed to convert instantly any continuous-suction pump to this type of action. It is constructed entirely from standard electrical and electronic components housed in a simple case (fig. 1).

Fig. 2 is a block schematic diagram of the apparatus. The cycle of operation requires that two automatic solenoid valves (SV_1, SV_2) be incorporated in the suction tube, and these are energised in turn to provide suction periods of 20 sec. separated by intervals of 2 sec. During these intervals the distal end of the suction tube is open to the atmosphere. A reservoir, having a volume at least three times that of the collecting bottle, is used in conjunction with the pump. This, together with the long suction period, permits the use of a small pump.

The control circuit is shown in fig. 3. The timing impulses, obtained from the transistor multivibrator (T_1, T_2) are fed to the driver transistors (T_3, T_4), which govern the operation of the solenoid valves. The pilot lamps (L_1, L_2), coloured green and amber respectively, give visual indication of the timing cycle. In the event of lamp failure the operation of the unit is unaffected. The power supply is a basic mains-operated bridge-rectifier circuit, giving an output of 24V and 0.5 amp.

The unit has proved reliable in use, and the nurses like its simplicity of operation.

We are indebted to Mr. Joseph Devlin for the photograph.

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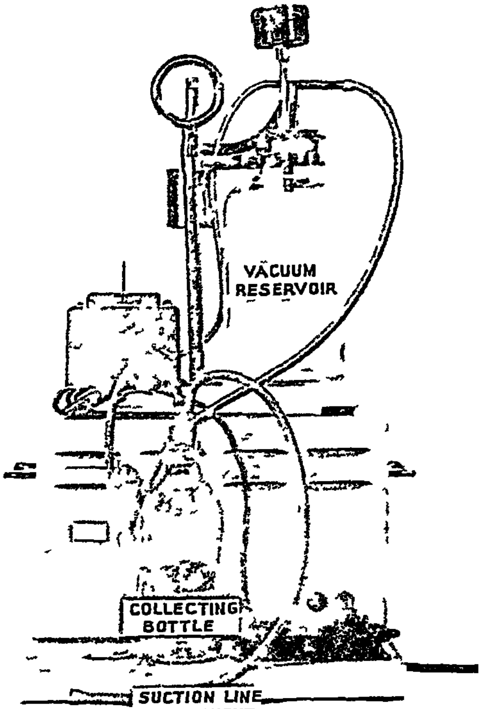

Fig. 1

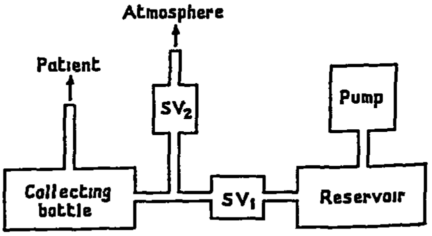

Fig. 2.

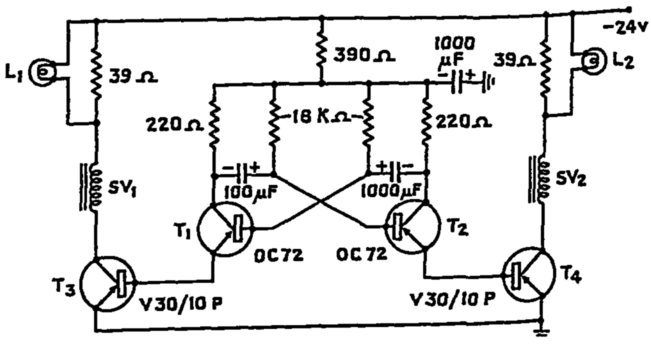

Fig. 3

Medical Societies

SOCIETY FOR SOCIAL MEDICINE

THE fourth annual meeting of the society was held in Oxford from Sept. 29 to Oct 1

Leukæmia

Dr **ALICE STEWART** (Oxford) propounded the view that many cases of stem-cell leukæmia in childhood have their origin in an inherited defect Children in the preleukæmic state (like mongols, who have an exceptionally high risk of developing leukæmia) are especially liable to die of pyogenic infections Hence both the number of deaths attributed to leukæmia and their age-distribution have been altered by the advent of antibiotics and by the declining incidence of these infections

Dr J A. H **LEE** (London) described a " bulge " in the age curve of mortality from leukæmia between the ages of 13 and 19 This is due to a temporary rise in acute myeloid cases, most notable in males, which is evident on both sides of the Atlantic, and can be traced back at least as far as the 1920s

Dr F W **GUNZ** (Christchurch, New Zealand) reported on a study now in progress which covers over 80% of leukæmia cases diagnosed throughout New Zealand. Although reporting is relatively incomplete in Maoris, chronic lymphocytic leukæmia is clearly less common in this group than in the population of European origin Compared with their controls the leukæmia cases showed a clear excess of exposures to radiotherapy and of personal histories of cancer, but at most 7% of all cases could be accounted for in terms of any recognised ætiological factors

In the discussion questions were raised about recent evidence conflicting with previous reports of an association between childhood malignant neoplasms and antenatal radiography Dr **RICHARD DOLL** (London) said that his own study, relating to leukæmia in children, had not confirmed this association, but that it could not be regarded as disproved.

General Epidemiology

A large body of data collected by the Veterans Administration in the U S A, was used by Dr E D **ACHESON** (Oxford) to demonstrate a rising incidence of multiple sclerosis from south to north, both between and within States, and applying to both white and coloured men as well as to veterans of both world wars Reasons were given for believing that this gradient did not merely reflect differences in diagnostic standards, and certain climatic variables (severity of winter, rainfall) could also be ruled out Preliminary analysis of mortality data from the southern hemisphere appeared to confirm the positive correlation between incidence of multiple sclerosis and latitude

Dr D **CAMERON** and Dr G D **FORWELL** (Edinburgh) had attempted a complete ascertainment of cases of diagnosed diabetes among the patients in 77 Scottish practices The overall prevalence was between 4 and 5 per 1000 population The prevalence estimates paralleled mortality figures in showing an excess of cases among manual workers in the younger adult age-groups, and an excess among non-manual workers at higher ages

A paper by Dr **DOLL** and Dr R E W **FISHER** (London) showed how detailed epidemiological analysis, supplemented by chemical study of air samples, had led to the inculpation of an old-fashioned type of retort as responsible for the excess of deaths from lung cancer among gas-retort workers In studies of this type one should not trust mortality expectations computed from national data to yield a standard appropriate to a selected industrial group, but occupational mortality-rates within the industry could be compared with some confidence

Pregnancy Hazards

Why do only a small proportion of the second and later rhesus-positive children born to rhesus-negative women develop hæmolytic disease of the newborn? This question was discussed by Dr E G **KNOX** (Newcastle upon Tyne), whose previous work had shown that maternal-fœtal ABO incompatibility tends to prevent sensitisation of rhesus-negative mothers Comparison of the obstetric details in a group of sensitising pregnancies with a control group indicated that toxæmia, surgical interference, and placental anomalies were among the factors which might pave the way for rhesus isoimmunisation in a later pregnancy

Dr R G **RECORD** (Birmingham) discussed variations in the incidence of anencephalus, which has shown a rising trend in recent years Though the variables implicated are to some extent confounded with one another, at least four (parity, maternal age, low social class, season of conception) can be shown to have an independent effect.

Psychiatry · Mental Abilities

Dr J K. **WING** (London) had conducted a study of male schizophrenic patients under the age of 60 who had been resident at two London mental hospitals for upwards of two years Though mental symptoms and most types of ward behaviour showed no significant trend with length of stay in this group, unfavourable attitudes to discharge were commoner in the longer-stay patients This was interpreted as reflecting a syndrome of " institutionalism ", possibly similar to a syndrome which has been described in other segregated communities

Six years after their discharge from mental hospital two-thirds of a group of patients were found to be " not ill from a psychiatric point of view " This favourable outcome was reported by Dr **LILLI STEIN** and Dr W **WARREN** (London) in their follow-up study of patients treated in the adolescent unit of the Bethlem Royal Hospital Relatively young patients (under 14 on admission) did well, as did those with neurotic rather than psychotic or organic disorders, but on an individual basis there was little association between prognosis at discharge and condition at follow-up

The influence of birth rank and family size on educational selection was discussed by Dr J W B **DOUGLAS** (Edinburgh), who produced evidence that the handicapping of later children and children from large families derived from environmental rather than genetic factors A measure of parental interest in the child, generally higher for children of small families, was found to correlate not only with performance at the ages of 8 and 11 but also with the progress achieved between these ages

Dr **MERVYN SUSSER** and Dr **ZENA STEIN** (Manchester) reported on a study of the social distribution of children classed as educationally subnormal Except when associated with brain damage this condition appeared to occur only in families belonging to what was characterised as a " demotic " —in contradistinction to an " aspirant "—subculture Data from other studies were adduced in support of the thesis that this type of mental retardation is due to environmental factors

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Reviews of Books

Doctors and Disease in Tudor Times

W S C **COPEMAN**, O B E., F.R C P London Dawsons 1960 Pp 186 42*s*

THEON, the mathematician of Alexandria and the last notable philospher of the Graeco-Roman era, died about A D 400 A kind of twilight descended on men's minds thereafter, and did not lighten for more than a thousand years Then, in 1543, two great works appeared, distinguished because they did not merely repeat old dogmas but contained new observations and were based on experimental methods One was Vesalius's treatise on human anatomy, and the other the *De revolutionibus orbium cælestium* of Copernicus The Dark Ages were over, and the Renaissance had begun

In this country, about the same time, the Tudor period began, and within that era Linacre founded the Royal College of Physicians, and Vicary united the Guild of Surgeons with the Barber's Company John Caius created one of our first medical schools and William Harvey went to study there. The significance of such times for the medical historian needs no emphasis Fortunately, they are abundantly documented, for the same era saw the wide development of printing indeed, the first volume ever printed in these islands, it is said, was a clinical study—von Hutten's subjective account of syphilis Most medical studies of the period are concerned with some particular aspect of Tudor medicine, and Dr Copeman's book is remarkable for its breadth

The first chapters deal with the status of the physician, his education, and the doctrines that he was taught The succeeding ones describe the diseases which confronted him, and the medicaments and instruments he could deploy against them A final section discusses public-health practices of the day Dr Copeman is clearly well versed in all the ordinary texts, on which his remarks constitute a useful and authoritative commentary The book contains in addition much information not easily found elsewhere how, for instance, a " vomit " was prepared by allowing wine to stand in an antimony cup for some days until it had become impregnated with tartar emetic Dr Copeman also describes the origin of our national dish of bacon and eggs and differentiates clearly between a seton and an issue, which is more than most dictionaries do

Atlas and Manual of Dermatology and Venereology

Prof W BURCKHARDT, director of the Municipal Policlinic for Skin and Venereal Diseases, Zürich Translated and edited by STEPHAN EPSTEIN, M D Baltimore Williams & Wilkins London Baillière, Tindall, & Cox 1960 Pp 281 112*s*

IN an atlas of dermatology which is intended for the practising dermatologist, illustrations of common skin diseases, however excellent, are a waste of money and space, but in an atlas designed for the student or practitioner with limited experience many photographs are needed to illustrate all variants of the commoner skin diseases The preface to the American edition of Professor Burckhardt's book makes it clear that it is intended for the non-specialist reader, yet the 73 illustrations and 99 colour plates can give only a glimpse of some aspects of each disease mentioned, and some common, as well as not so rare, diseases are not illustrated at all The illustrations and colour plates, drawn mainly from *Folia Dermatologica*, are of the highest quality, but space could have been saved and used for additional illustrations if the size of some had been reduced

Undoubtedly it is difficult to select the correct material to include in a textbook of this kind, but some commoner conditions, such as scurvy as a cause of purpura, have been omitted while comparative rarities have been mentioned The 29 pages on venereal diseases give a clear succinct account of the main problems which may be met in general practice Dr Peter Smith has supplied information about medication in Britain The therapeutic advice given is sound even if some proprietary names may be unfamiliar to British readers

Report of the First Institute on Clinical Teaching

Editors HELEN HOFER GEE, JULIUS B RICHMOND Evanston, Illinois Association of American Medical Colleges 1959 Pp 233 Cloth $3 00, paper $2 00

THE 1958 " institute " of the Association of American Medical Colleges was the first of two devoted to clinical teaching It was organised on similar lines to those held every year since 1953 The main subject was broken down into several topics, and on each of these many factual data were collected from the medical schools by the research division of the Association The discussions started by the main speakers therefore were based not only on personal opinions and experience but also on a reasonable quantity of relevant facts

The main subjects were the objectives of clinical teaching, the setting of clinical teaching, the student, the patient, and the teacher, and extramural forces influencing medical education The last topic included a symposium entitled " Other disciplines look at Medicine ", with papers from a philosopher, an economist, and a behavioural scientist The report also includes the principal papers on each " topic ", together with the data collected by the research division It offers the British reader interesting and even provocative views on the aims and methods of clinical teaching, and on the functions of university hospitals It also provides a reference book on almost every aspect of clinical medical education in the United States and Canada. The types of hospitals and even patients are listed, with details of curricula, forms of experience offered to students, and a sample of staff and student opinion on all these things The financing of clinical teaching, the methods of control over it exerted by the schools, and the methods of selecting teachers and of appointing clinical staff are also set out, and generally make a very interesting comparison with our own methods

The quantity of information here is vast and by no means all of it is relevant to Britain, but those responsible in this country for the organisation of clinical teaching will find much that is challenging, though perhaps less that is comforting, for they can hardly fail to note how little authority they have compared with those responsible for teaching in North America The British clinical teacher whose responsibility is more limited and personal will also find much of interest, and if by chance he is one who knows all there is to know of this complex subject by intuition, inheritance, or other forms of internal revelation, he will be intrigued to find how many teachers exist to whom some quite different convictions have been given, and that there are others who are still searching for some of the answers

Congenital Malformations (London J & A Churchill 1960 Pp 308 45*s*) —This book, edited by Dr G E W Wolstenholme and Miss Cecilia O'Connor, is the text of a notable Ciba Foundation symposium, held in January this year, on the ætiology of congenital malformations, with Prof W J Hamilton in the chair Prof Thomas McKeown reports the incidence of malformations in the city of Birmingham over the three years 1950–52, and relates this to the incidence found in other large series Dr A C Stevenson describes the association of hydramnios, not only with anencephaly and gut obstructions, but with a large variety of malformations Prof L S Penrose discusses the genetical causes of malformations, and Dr C E Ford describes the recent advances that he and others have made in the recognition of chromosome abnormalities in certain classes of malformed children Then Dr T H Ingalls gives a general account of environmental agents causing malformations in man A series of remarkable papers follows showing the variety of chemical agents which may induce fœtal malformations in laboratory animals These include tumour-inhibiting chemicals, such as the alkylating agent chlorambucil, antimetabolites, such as the folic-acid analogue aminopterin, antibiotics, such as actinomycin D, and even hypervitaminosis A, which, as Prof A Giroud reports, will produce in rats and mice malformations very similar to human anencephaly It should not be long before some of this careful and elegant experimental work finds practical application in antenatal pædiatrics

The Mechanism of Action of Insulin. (Oxford Blackwell Scientific Publications 1960 Pp 320 32*s* 6*d*) — This volume is a record of a symposium convened in September, 1958, by the British insulin manufacturers in London Many prominent research-workers from North America and the Continent, as well as from Britain, took part In his introductory remarks the chairman, Prof F G Young, invited those present to " let their hair down ", and this exhortation contributed to a friendly informality and free speculation which make the book stimulating to read The subjects discussed ranged more widely than the title of the symposium suggested, and they included the chemistry of insulin, bioassays of insulin, insulin antagonists, the mechanism of the hypoglycæmic action of salicylates, thiol substances and the sulphonylureas, and prediabetes in pregnancy, but even on the subject of the mechanism of action of insulin the text reveals much that is controversial even after the research of nearly forty years The symposium was a success, and this record, edited by Mr W A Broom and Dr W F Wolff, is valuable as an integration of so many areas of diabetic research related more or less closely to insulin

THE LANCET

LONDON 15 OCTOBER 1960

Tranquillisers in Psychiatry

THE *bon mot* describing chlorpromazine as a substance having only side-effects has been conclusively proved wrong: clinical reports from many countries have now confirmed the original observations by DELAY and DENIKER[1] on its value in the treatment of schizophrenia. Concurrently reserpine was shown to have similar indications in psychiatric practice.[2] The era of tranquillisers, a generic term coined to distinguish these drugs from traditional sedatives, has begun: by definition they act on the emotional state without affecting clarity of consciousness. It is a somewhat grandiloquent and not strictly accurate term, but it is probably here to stay.

Many phenothiazine derivatives[3] have been devised by modification of the chemical structure of chlorpromazine, and other supposedly beneficial, though chemically unrelated, drugs, have been marketed for the treatment of mental illness. This abundance of riches for the traditional poor relation of physical disease is welcome, but some of the new compounds have been introduced without full enough clinical experience of them for their therapeutic value and toxicity to be confidently appraised. Since the ætiology of mental disorders is still largely unknown, theoretical consideration or observations on animals form only a tentative basis. In psychiatry even more emphatically than in other branches of medicine, clinical results remain the final arbiter of effectiveness and safety. Enthusiasm seems to be running well ahead of evidence, and it is reported that in 1958 alone the sale of these drugs in the U.S.A. exceeded £70 million.[4]

Chemically the tranquillisers can be divided into three groups: reserpine, the phenothiazine derivatives, and drugs of varied chemical structure, such as meprobamate, benactyzine, and methaminodiazepoxide. Reserpine, although often very effective in the treatment of severely disturbed and overactive patients, has autonomic effects; and it is being gradually replaced in psychiatric practice by phenothiazine derivatives. These differ among themselves in the nature of the side-chain attached to the phenothiazine nucleus: the dimethyl subgroup, including chlorpromazine and promazine, and the piperazine subgroup, comprising perphenazine and trifluoperazine, are the two most important. Thioridazine, which has a thiomethyl radical substituted in position 2 of the phenothiazine nucleus, is in a category by itself. The drugs differ in dosage and toxicity. Among the most dangerous toxic effects are agranulocytosis, hypotension and vascular collapse, increased liability to thrombosis, hepatic dysfunction, convulsions, and depression[5]; these toxic effects are rather commoner with the dimethyl subgroup. Sedation is also commoner with this subgroup, of which chlorpromazine is still the most widely used, and they are therefore preferred in the treatment of conditions characterised by overactivity. Piperazine derivatives, of which trifluoperazine is probably the most widely used, tend to produce motor restlessness and anxiety—symptoms for which American workers have adopted the term akathisia originally applied by SICARD[6] to similar manifestations in post-encephalitic parkinsonism. Extrapyramidal symptoms, a side-effect common to all phenothiazines, appear generally earlier with the piperazine subgroup, which seems particularly effective where delusions are the central feature of the illness. Thioridazine, not as yet widely used in this country, is said to have many of the sedative properties of chlorpromazine, but with fewer side-effects and negligible toxicity.[7]

As regards the third (miscellaneous) group of tranquillisers, opinion is unanimous only about their ineffectiveness in schizophrenia. They are claimed to be useful in a large variety of psychological disorders generally termed neurotic, particularly those in which anxiety is prominent. In this large and ill-defined clinical area the abnormal merges imperceptibly into what has to be regarded as normal. Therapeutic studies should therefore be carefully designed and cautiously judged. Yet the claims made are often based on uncontrolled trials, and in controlled trials[8 9] positive results have either been very modest or totally absent. Most psychiatrists would therefore agree that tranquillisers have proved a failure in the treatment of neuroses.[10] Only time will tell whether methaminodiazepoxide, one of the latest additions to this group, will be more successful than its forerunners. Unfortunately, the reports so far published[11] are uncontrolled and correspondingly less convincing. A fortnight ago Dr INGRAM and Dr TIMBURY,[12] impressed by the troublesomeness of side-effects, suggested that meanwhile this drug should be used with circumspection. Correspondence last week[13] and in the present issue shows that, in the experience of others, side-effects have been less common and severe. But on the existing evidence the therapeutic usefulness of this drug cannot be regarded as established, and toxic effects, such as ataxia, dermatitis, and rage reactions,[12] suggest a need for caution.

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[13] Jenner, F. A., Kerry, R. J., Parkin, D. *ibid.* Oct. 8, 1960, p. 816.

Although chemically unrelated, both reserpine and the phenothiazines are effective in the treatment of schizophrenic conditions, and both are liable to produce extrapyramidal symptoms. The frequent association of clinical improvement with drug-induced parkinsonism[14] has led some to regard the two as necessarily linked[15] and has inspired interesting speculations on the pathological basis of schizophrenia. But these two effects are not strictly parallel, and the suppression of extrapyramidal side-effects by drugs does not apparently impair therapeutic efficacy. From the clinical, and possibly the neurophysiological, point of view it nevertheless seems reasonable to group reserpine and the phenothiazines together, separating them from the third group—the tranquillisers pure and simple. Another designation, such as neuroleptic[16] or neuroplegic,[17] might be more appropriate for reserpine and the phenothiazines.

The efficacy of reserpine and the phenothiazines in many acute and some chronic schizophrenic illnesses has raised the question whether they intervene in the abnormal biochemical processes which many believe underlie schizophrenia. Reserpine sedation is generally believed to be related to the depletion of cerebral biogenic amines, in particular serotonin and noradrenaline.[18] The phenothiazines, like biogenic amines, have three carbon straight chains with a terminal nitrogen atom; possibly these drugs compete with the amines for receptors in the central nervous system, thus preventing the actions normally exerted by the amines.[19] The blocking of serotonin and noradrenaline achieved, through different mechanisms, by both reserpine and the phenothiazines may account for their largely similar effects in psychiatric treatment. This relationship of known pharmacological properties to clinical efficacy cannot yet be regarded as established, and a biochemical mythology of mental disorder, based on tempting but largely unsubstantiated speculations, might clearly prove harmful in the long run. But the systematic exploration of hypotheses based on known pharmacological actions, coupled with critical appraisal of drug therapy in clinical practice, may lead to a better understanding of the physiopathology of mental disorder and open the way to its rational treatment.

Heatstroke

THE mode of onset of heatstroke has not been clearly established. The two main issues are whether cessation of sweating precedes or follows hyperpyrexia, and whether circulatory failure is or is not a constant and important feature. One reason for the continuing doubt on these questions is that in heatstroke, which is one of the most urgent of all medical emergencies, treatment has priority over investigation, while the high mortality even with rapidly effective cooling rules out experimental induction of the condition in man. Another reason is that heatstroke is often a catastrophe of sudden and unheralded onset, and not the climax of several days' debility, pyrexia, and diminished sweating.

A hypothesis which bids to answer both the main questions at once has been propounded by Gold,[1] who has made important observations on the development of heat pyrexia in men exposed in the laboratory to dry heat, some for two hours at 54·5°C (130°F) and others for one hour at 71·1°C (160°F). He has confirmed that exposure to severe heat is accompanied at first by a hyperkinetic circulation and a raised cardiac output, and in several subjects he found considerable rises of pressure in a forearm vein. He observed a quantitative correlation between the rise in venous pressure and what he describes as effective body-heat storage, which appears to be a partly theoretical assessment of heat gained by the body despite maximum operation of heat-dissipating mechanisms. Each subject was removed from the hot chamber when collapse was judged to be imminent, on the basis of abnormal sensations such as light-headedness, and of a facial colour change from pinkish-red to almost ashen grey. At this point many of the subjects began to cease sweating. Gold suggests that the primary event in the circulatory collapse of heat pyrexia is high-output cardiac failure, and that the cessation of sweating results from the rising venous pressure.

A pronounced increase in the circulation through the skin and a rise in cardiac output are normal responses to extreme heat. In this sense these features, and presumably also a rise in forearm venous pressure, will precede heatstroke. But, although his subjects were exposed to sufficiently high temperatures, it does not necessarily follow that Gold succeeded in his attempt to observe the pre-heatstroke state in the absence of hyperpyrexia the features of light-headedness and ashen-grey face which he describes are akin to the simple heat collapse or syncope first recorded by Dreosti,[2] which is a much more common heat syndrome than heatstroke. In heatstroke the face is typically red, and sometimes congested and cyanosed as if the patient had been strangled, and less commonly it is grey through circulatory collapse, which is usually regarded as a late and prognostically ominous result of hyperpyrexia. Ferris et al.[3] sought, but failed to find, evidence of cardiac failure in 36 patients with heatstroke who had no history of poor cardiac function, and observed peripheral circulatory failure or shock in only 7 of 34 patients. In 7 patients with rectal temperatures above 41·7°C (107°F) they found normal pressures in the femoral vein. Austin and Berry[4] observed that in 27 of 100 cases of heatstroke the systolic blood-pressure was below 100 mm Hg, but in these cases the state was distinguishable from the usual picture of peripheral circulatory collapse in that the patients had a hot, dry skin and bounding pulse. It seems likely that when circulatory collapse does develop in a patient with heatstroke, it is preceded, as **GOLD** suggests, by high-output cardiac failure, but on clinical grounds it must be regarded as a complication and not as an early feature of heatstroke

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[3] Ferris, E B, Blankenhorn M A, Robinson, H W, Cullen, G E *J clin Invest* 1938, 17, 249

[4] Austin, M G, Berry, J W *J Amer med Ass* 1956, 161, 1525

In reporting that his subjects began to cease sweating when they were near to collapse, **GOLD** makes an unsupported prediction A measurable decline in sweating after an hour or two in severe heat has been recorded by others For want of a specific term, this feature has been called sweat-gland fatigue, and so far no wholly satisfactory explanation has been found **LEITHEAD** and **PALLISTER**[5] have found that sweating is progressively reduced by depletion of body water, and **BANNISTER**[6] has reported that after intravenous injection of bacterial pyrogens sweating ceases temporarily Apparently both dehydration and infection may predispose to heatstroke, although neither is a necessary prelude Whether sweat-gland fatigue, which is known to be independent of dehydration, plays an important part in the onset of heatstroke is undecided A person who seems to have stopped sweating—who, in other words, has a completely dry skin when those around him sweat profusely—is not necessarily on the verge of heatstroke **SARGENT** and **JOHNSON**[7] observed a man first on a day in which he developed abnormally dry skin and weakness and giddiness while marching in a hot climate, and secondly on the following day when, still with a dry skin, he resumed marching He marched at 3 75 m p h for 1 5 miles with a peak rectal temperature of 38 5° (101 4°F) and an evaporative fluid loss of 850 ml per hour—which implies that sweating occurred

In support of his suggestion that a rise in venous pressure may account for the cessation of sweating so characteristic of heatstroke, **GOLD** draws an analogy with the observation by **BURCH**[8] that thermal sweating is diminished in congestive cardiac failure Such an analogy is justified only if, in terms of increased venous pressure, exposure to severe heat has much the same effect as congestive cardiac failure coupled with exposure to the moderate heat—40°C (104°F)—employed by **BURCH** And if this assumption is correct, there remains the question of why a rise in venous pressure should cause a reduction in sweating The decline in sweating in congestive cardiac failure may be an expression of the associated sodium and water retention and hyperaldosteronism, a similar mechanism has been suggested for the reduction in sweating which accompanies dehydration[5]

A clear understanding of the onset of heatstroke will surely come, but to expect the incidence to be reduced thereby would be unrealistic Proper application of what is already known of the principles of prevention would make heatstroke in controlled communities, such as Servicemen, less common than it is, and, in areas where heatstroke is known to occur, devices for effective cooling, such as that described by **GUTHRIE** and **MCCRACKEN**,[9] should be at hand

Community Mental Care?

APPREHENSION, as well as hope, accompanies those developments in psychiatry which have latterly been called "community mental health" The doubts represent not merely an awareness of practical difficulties but also much deeper feelings which have always coloured the attitude of society towards mental illness The term "alienist" indicated the function allotted to psychiatry—to remove out of sight, into a locked security, those whose departure from normal patterns constituted a problem outside This problem is not only one of disturbed behaviour it also includes the anxiety aroused in any society by the deviant and by unrestrained emotions in the mentally ill Thus it was that the service which took care of the insane became almost completely isolated from the main currents of medicine—both preventive and therapeutic General hospitals, family doctors, and the public-health services had no more part to play in this custodial care than the mental hospitals generally had in the problems of emotional conflict, and the first big break in this isolation did not come till the introduction of the National Health Service The tripartite character of the new regime made progress slow, and so did antiquated legal forms, but about the same time effective treatment became a reality for much of psychiatric illness, and its benefit was seen both directly and in the extra confidence given to psychiatric staff At the same time again, and largely through these changes, the public's attitude of fear and suspicion began to alter

Today, in a period marked by the introduction of the Mental Health Act, the overwhelming need is for integration of the different services involved, and this theme was embodied in a quadripartite conference held last week by four bodies which have equally important parts to play in the progress of mental health—the Central Council for Health Education, the College of General Practitioners, the Royal Medico-Psychological Association, and the Society of Medical Officers of Health

Education in mental health was a major subject, and, though education of the public was mainly discussed, dissatisfaction with the place of psychiatry in medical training was generally expressed Even if psychiatry is adequately taught as a subject, its approach is generally ignored in the other departments of teaching hospitals, and this deficiency is felt alike by family doctors and by those in public health who want to do their part in a comprehensive mental health service Discussing public attitudes, Dr I G **GORDON-SMITH** pointed out that community care may be impossible if the fears and fantasies of significant relatives are ignored, and, in dealing with the attitudes of those relatives who are decisive in the patient's environment, social workers can sometimes change the situation As for the patient, his attitude towards a psychiatric illness presents an illuminating contrast with that towards a socially approved illness, such as appendicitis An acute feeling of guilt is likely to be present, based on the conviction that the illness would have been avoided if he had exercised more effort or responsibility, and the belief that it is hereditary may result in his waiting anxiously for it to appear in all the other members of the family. Explanation that such emotions as hate, fear, and guilt are part of the normal mind may come as a revelation, but are quite likely to arouse resentment or rejection. Another speaker said that viewers' letters, following the B B C television series "The Hurt Mind," showed that the public stereotype of mental illness includes violence as its main feature. This feeling of people around him that he may erupt into an aggressive outburst at any moment must clearly be a matter of concern to the psychiatric patient. Methods of mental-health education, described by Dr A J Dalzell-Ward, lay stress on social skills, such as parentcraft and the fostering of good personal relationships, aiming to make use of personality assets. As with other preventive measures, their direct effects are almost impossible to measure, but there can be no doubt of the need they try to satisfy.

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[5] Leithead, C S Pallister, M A *Lancet* July 16 1960 p 114
[6] Bannister R G *ibid* p 118
[7] Sargent, F Johnson, R E *ibid* 1960 i 1018
[8] Burch G E *Amer J med Sci* 1946 211 181
[9] Guthrie, J, McCracken, A V *Lancet* 1960 i, 682

Attitudes were also mentioned in the account of rehabilitation and resettlement, by Dr J K Wing. The functional disability caused by disease may do less harm than the patient's own attitude towards it, or the social handicaps imposed by other people. In mental hospitals, increase in the length of stay seems to be related to a steady lessening both of the desire for discharge and of the contacts maintained by relatives. It is estimated that nearly half of long-stay schizophrenics (who form 70% of the whole long-stay population) have given up all thought of returning to the community. Yet many such patients who have stable behaviour and only moderate symptoms are capable of a useful day's work—given the necessary change of attitude. It is noteworthy that the acute case coming into a mental hospital enters a culture profoundly influenced by the character of its long-stay wards: there cannot be a full community service unless admission for psychiatric treatment is readily accepted by the public, and this will not occur until the long-stay wards are therapeutic rather than custodial. But community care can be truly preventive, by discovering and treating psychiatric illness at an early stage, before the tolerance of relatives has been strained to its limit, and this may be an answer to some of the fears expressed.

Dr Wing said that current follow-up studies by the Medical Research Council of discharged schizophrenics in London showed that aftercare arrangements are very far from complete. Many do not keep follow-up appointments or bother to take further medication. It is clear that the main burden of their care is falling on the family doctor, and this was emphasised also by Dr S I Abrahams. The family doctor is the one who bears a continuing responsibility for the patient and who must coordinate the services applied. If he cannot do so, the patient may receive piecemeal or even conflicting attention, which ignores him as a person. Nobody, however, has the responsibility of making the family doctor aware of the many services—Government, local-authority, and voluntary—which may help him. Dr Abrahams described how he began to meet regularly the health visitors who worked in the area of his practice, and how he discovered that their activities had been almost completely unknown to him before. That available services should be fitted to the needs of the individual patient was stressed by Dr I G Davies, of the Ministry of Health. In community care, it is necessary to apply the whole range of legislation comprehensively, rather than try to put the patient in a single compartment. Expert clinical and social guidance is needed to deploy these services so that help can be given most effectively, and there should be a well-defined chain of clinical command. The quality of services provided, Dr Davies said, would greatly influence the tolerance of the community and thus the success of community care.

Over and over again this conference returned to attitudes and their importance. Attitudes of the public to mental illness in themselves and others, of psychiatrists to their patients, both acute and long-stay, of doctors and health workers to their colleagues in other services (many of whom may now be unknown to them), and of families to those public services which aim to help them. Education and cooperation were the measures called for to deal with long-established patterns of rejection and isolation.

Renal Papillary Necrosis

Renal papillary necrosis is an ischæmic infarction of the medullary pyramids, often confined to the papillæ, sometimes involving the more central part of the pyramid, but never extending to the cortex or to the interpyramidal medulla, thus the term "papillary necrosis" probably indicates the site of the lesion better than "medullary necrosis". Because the condition is often accompanied by infection it was commonly called necrotising papillitis, but inflammation is not always present. Two articles have brought together much of the widely scattered information about this disorder. In the first of these, Lauler et al[1] describe 5 cases, and analyse the clinical features of 250 histologically proved cases (mostly acute fulminating or at least subacute), while in the second Lindvall[2] reports in detail the X-ray appearances of 155 more chronic cases examined during life.

In 1877 Friedreich[3] first described necrosis of the renal papillæ in a man with enlarged prostate and hydronephrosis, and a few years later Turner[4] reported instances in patients with tuberculosis, rheumatic carditis, and diabetes, establishing its association with back-pressure on the renal pelvis and sepsis and its occurrence in each sex and in both diabetic and non-diabetic patients. For the next fifty years little further was heard of the condition, and then from various countries came reports of series of cases mostly emphasising its close association with diabetes—especially when complicated by acute pyelonephritis, though it was suggested that the necrosis was a form of diabetic gangrene.[5] This period coincided with the prolongation of life of diabetics. LINDVALL[2] shows that such cases are now less common, but they will continue to arise because some diabetics will always default, especially in notifying complications. In most non-diabetics with papillary necrosis, increased intrapelvic pressure and secondary infection were found. DAVSON and LANGLEY[6] pointed out that, if increased pressure on the blood-vessels of the pyramids was the sole cause of the necrosis, it was surprising that this was not commoner in hydronephrosis, but later evidence of the healing of necrosed tips[7] suggests that the well-known X-ray appearance of flattening of the papillæ in hydronephrosis may represent the end-result of papillary necrosis. While in most such cases the patient is elderly, because of the causal conditions, the disorder is also found in children in association with acute lesions. STIRLING[8] reported 2 instances in acute pyelonephritis, a 3rd in renal-vein thrombosis, and a 4th with small arterial infarcts and thrombosis of venous radicles, and MARKS[9] has lately reported the condition following exsanguination in infancy. Thus infection by itself or poor circulation by itself may cause the necrosis.

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[1] Lauler, D P, Schreiner, G E, David, A *Amer J Med* 1960, 29, 132.
[2] Lindvall, N *Acta radiol, Stockh* 1960, suppl 192
[3] von Friedreich, N *Virchows Arch* 1877, 69, 308
[4] Turner, F C *Trans path Soc Lond* 1884–85, 36, 268 *ibid* 1885–86, 37, 290, *ibid* 1887–88, 39, 159

In the past eight years there have been reports in Switzerland and Scandinavia[10] of a great increase in the number of cases of papillary necrosis following excessive use of phenacetin compounds. In LINDVALL's series of 155 patients examined radiologically for changes indicating renal papillary necrosis, there were relatively few with diabetes or chronic urinary obstruction, and the majority had taken phenacetin in such quantities as possibly to lead to damage. In all the kidneys examined histologically, either after resection or post mortem, the changes of chronic pyelonephritis, often with acute exacerbation, were found just as in the diabetic and obstructive cases. The phenacetin may have been taken owing to the obscure symptoms of the pyelonephritis, though LINDVALL admits that phenacetin may render the kidney more susceptible to infection. It is perhaps fortunate that in this country aspirin, and not phenacetin, is the main constituent of headache powders.

Other factors suggested as causal, such as drugs,[11-13] toxins (coliform or staphylococcal), or disordered fat metabolism, have been less clearly substantiated. Some of these act on the vascular supply. BAKER's[14] work on the blood-supply of the renal papilla shows how vulnerable this is to diabetic arterial disease, infection, and back-pressure on the calyces. One source of supply is the vasa recta coming down from the juxtamedullary glomeruli; in diabetes or chronic pyelonephritis many of these may be fibrosed, while in infection the vessels are liable to septic stasis. The other source is branches from the plexus of spiral vessels in the calyx, these branches running over the fornix of the lesser calyx and back superficially to the apex, thus being liable to periarteritis and endarteritis in infection and to obstruction in back-pressure.

Papillary necrosis manifests itself in no special clinical syndrome, the symptoms and signs being those of the associated and causal disease. But suspicion may be aroused by colic due to ureteral passage of the necrotic material, and the surest diagnostic sign is the finding of such material in the urinary sediment. The possibility of diagnosis by renal biopsy[1] should perhaps be regarded with reserve. In the more chronic cases, where urography is not liable to increase back-pressure on the pelvis, LINDVALL[2] has shown that, with highly selective contrast medium, intravenous pyelography can reveal definite "ring" changes in the renal papillæ, formation of cavities in the pyramids or at the papillæ, and the outline of concretions formed round necrotic fragments.

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[5] Edmondson, H A, Martin, H E., Evans N Arch intern Med 1947, 79, 148
[6] Davson J Langley, F A J Path Bact 1944 56 327
[7] Schourup K. Acta path microbiol Scand 1955 44 168
[8] Stirling G A. J clin Path 1958, 11, 296
[9] Marks, I M Lancet Sept. 24, 1960, p 680
[10] See Lancet 1959, i, 84
[11] Levaditi, C. Arch int Pharmacodyn 1901, 8 45 Mandel, E E., Popper H Arch Path 1951 52 1
[12] Rehns J Arch int Pharmacodyn 1901 8 199
[13] Oka A Virchows Arch 1913 214 149
[14] Baker S B deC. Brit J Urol 1959, 31, 53

Annotations

THE LEADERS AND THE LED

SINCE scientific research became a popular and even reputable way of earning a living, its motives, organisation, and rewards have been favourite subjects for orations. Most of these are heard, praised, and forgotten. Research continues because some men are incurably curious, some ambitious, and some slaves to conformity; today it is not a hobby pursued in the intervals of teaching but a way of life which (some would say) must be interrupted as seldom as possible by more banal duties. Nevertheless it has its problems, and a lecture given at St Andrews by Sir Lindor Brown[1] deals with one which is not the less important because it can be solved by no general rule. Sir Lindor's tenure of a chair in a department once graced by Bayliss, Starling, and Hill not only has made him the intellectual father of pupils all over the world but must have provided ample material for thought on the relations between "the chief" and his juniors in the research laboratory.

Analogy is a dangerous tool in argument, but the similarities between scientific research and the creative arts is too striking to be overlooked. In painting and science alike, there are basic methods which are best learnt at the master's feet. The beginner will want advice on the choice of a subject which will be within his powers and which will have a foreseeable end. (The scientific homologues of Haydon's gigantic canvases are seldom published.) The artist and the scientist both know the alternations of hard dull work, of despondency and idleness, and of what must be called—for want of a better word—inspiration. It is general experience, too, in both faculties that the tiro does better if he spends his days among others of like interests. Old men may be solitary by choice and remain productive, but the young learn more by coffee-housing with their fellows. All this throws great responsibility on the professor, and it is with him and his problems that Sir Lindor is concerned

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[1] The Perils of Leadership in Science. Sir David Russell Memorial Lecture University of St. Andrews. By Sir LINDOR BROWN, F R S London Oxford University Press 1960 Pp 20 3s 6d

But, as he says, the same problem arises whenever there is a difference of age and experience between two members of the same department, and it will always be complicated—sometimes beyond solution—by personal whims and antipathies.

In England and the United States professors are often regarded very much as other men. In Scotland their title counts for more, while in middle Europe they have power and fame beyond the dreams of the most ambitious savant here. The advantage, probably, is with the English student. Some things he must temporarily take on trust, but it will be better for him if these are derived from sources wider than the infallible wisdom of one great man. (The pains of disillusion can be very real.) Even in England there is wide diversity in the relations between the professor and his pupils. He may welcome them kindly, suggest—very diffidently—a programme of work, and then disappear for six months into a maze of committees, congresses, and delegations. He may on the other hand direct their labours so diligently and minutely that they are led to regard themselves as so much cheap labour. It is said that in one university department no research assistant is allowed to discuss his work with any colleague: all the strings lead back to one pair of hands, the professor's. Sir Lindor suggests—and experience supports him—that the best teacher is one who still finds time to work at the bench with his own hands. It is a comfort to the beginner to see that the experiments of a revered elder may end in abysmal failure on occasion. A daily comment may save hours of useless toil. Above all, the beginner will learn that research is something more exciting than mere work: it can, in fact, be fun.

Buonaparte said that no man can give orders to more than six subordinates, and on the whole a small department is a better place for learning than a large one. No man—not even the most distinguished Herr Geheimrat Professor—can advise expertly on every branch of a subject such as physiology, and it is better that the pupils be assigned to the care of those who are engaged in active research in their province. But the professor's responsibilities do not end there. He has seen more, read more, and thought more than anyone else in the department, and the pupils may find that even infrequent visits from Olympus will bring flashes of enlightenment. One may add that the outstanding teachers seem to share one quality which is seldom made public until their obituary notices are written: they earn the personal devotion of their pupils to the point of idolatry. Outsiders can sometimes get a hint of this from their nicknames.

POLIOMYELITIS AND THE BRAINSTEM

THREE physiological mechanisms in the brainstem may be involved by poliomyelitis—the lower motor neurones, the respiratory " centre ", and the circulatory " centre ". The motor nuclei in the brainstem are analogous to the anterior horn cells of the spinal cord, and it is therefore not surprising that they may be affected. One result of involvement of these nuclei is paralysis of swallowing, and, if care is not taken to protect the airway, the patient may die. If he survives, the power of swallowing almost always recovers. Involvement of the respiratory and circulatory " centres " is less easily evaluated. This is partly because these " centres " are not sharply localised regions like the cranial nerve nuclei, and, despite recent progress,[1] their various parts are not yet clearly mapped anatomically or understood physiologically. They constitute, however, part of the reticular formation of the brainstem, and there is ample evidence that poliomyelitis can damage this.

It has long been supposed that respiratory failure in poliomyelitis may be due to involvement of the respiratory centre, and irregularity of respiration is usually regarded as one of the principal diagnostic features. Bower,[2] however, with an enormous experience of poliomyelitis in California, states that in most cases with so-called respiratory-centre involvement this centre is not involved at all. The more carefully the patient is examined, his airway kept clear, his breathing assisted, and his electrolytes maintained at normal levels, the less commonly is involvement of the respiratory centre invoked to explain the clinical signs. In the great majority of cases respiratory failure in poliomyelitis is due to paralysis of the respiratory muscles—that is, to involvement of the thoracic part of the spinal cord and the fourth segment of the cervical cord from which the phrenic nerve arises.

Patients with poliomyelitis are subject to circulatory disturbances. Spencer et al.[3] indicate that such disturbances arise in about a third of patients with acute life-threatening poliomyelitis, but the ætiology is very varied and in acute cases it is usually difficult to distinguish the parts played by hypoxia, hypercapnia, alterations in tissue electrolytes and pH, myocarditis, lesions of the circulatory centre, and the effects of artificial respiration. When the acute phase of the disease is over, many of these factors cease to be important, but, as has been known for years, patients who have had poliomyelitis are liable to hypertension.[4] Zimanyi et al.[5] in Hungary have studied 336 bedridden patients in whom poliomyelitis had developed at least twelve months previously: 26% had hypertension. The incidence was highest in those who were most extensively paralysed, in those who had required artificial respiration, and in those with encephalo-bulbo-spinal, as opposed to purely spinal, disease. Zimanyi et al. argue that the hypertension is due to an alteration in the central nervous mechanisms controlling the blood-pressure—in short, to involvement of the circulatory " centre ". They also emphasise, however, that extensive wasting of muscle entails a decrease in the vascular bed, and therefore an increase in total vascular resistance. In health a rise in blood-pressure following increased total vascular resistance is prevented by reflex reduction in cardiac output, which restores the blood-pressure to normal. When the healthy subject is at rest, vascular resistance to blood-flow through the muscles is great and yet the blood-pressure is not raised, and it is improbable that in poliomyelitis the total vascular resistance is so much increased that reflex responses cannot compensate for this increase. Another explanation for persistent hypertension in poliomyelitis is renal infection. In severe cases of poliomyelitis catheterisation of the bladder is usually required, and urinary infection is common. In the Hungarian study, however, patients with suspected urinary infection were excluded. Riley and Knight[6] showed that of 60 patients with severe paralysis due to poliomyelitis, 44 had urinary infection and 10 had persistent diastolic hypertension. They were, however, reluctant to associate these two complications closely, for they could not correlate the severity of urinary infection with the appearance of hypertension, and in cases where the time of onset of hypertension was known it was earlier in the course of the disease than would be expected if it had resulted from renal infection.

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[1] *Physiol. Rev.* 1960, 40, supplement 4, pt. 2.

[2] Bower, A. G. Diagnosis and Treatment of the Acute Phase of Poliomyelitis and its Complications. London, 1954.

[3] Spencer, A. W., Jackson, R. R., Vallbons, C., Harrison, G. M. *Amer. Heart J.* 1960, 59, 384.

[4] Weinstein, L. *Circulation*, 1957, 15, 735.

[5] Zimanyi, I., Prohaszka, M., Szondy, M., Ormai, S. *Acta med. scand.* 1959, 164, 497. See *Lancet*, 1959, ii, 120.

[6] Riley, H. D., Knight, V. *Medicine, Baltimore*, 1958, 37, 281.

It seems that poliomyelitis can indeed affect the circulatory and respiratory " centres ", but it is probably unwise to diagnose such involvement except with great circumspection.

A FRESH START FOR THE SCHOOL DENTAL SERVICE?

THE deplorable state of the school dental service was mentioned by Mr Duncan MacGregor[1] in his presidential address to the British Dental Association, when he declared that the dental welfare of children was a " national scandal " The situation is becoming worse, and nothing effective is being done to make it better Perhaps action will be expedited by a report[2] in which the British Dental Association describes the service's rise and present decline

The first school dental clinic was opened in Cambridge in 1907, but not until the passing of the Education Act, 1918, were local authorities obliged to provide dental treatment for schoolchildren In 1936 the Board of Education recommended that there should be 1 dentist for every 5000 children in urban areas, and 1 for 4000 in the country More recently, the Minister of Education has suggested that, for a complete dental service, 1 dentist for every 3000 children is needed Actually, since 1938, when in England and Wales there was 1 dentist for 5300, there has been a steady fall in numbers, except in 1947, when the ratio was 1/5000 1957 was the worst year (1/8000), and since then the position has improved slightly (1/6800 in 1958) But there is no sign of any sustained increase, and the ideal ratio of 1/3000 seems completely unattainable As for dental treatment for nursing and expectant mothers, and preschool children, the British Dental Association says that " the title 'priority dental services' has no meaning at all in practice " In fifteen years, it is estimated, 45% of the present full-time dental officers will have retired, and the chances of filling their places seem remote

Apart from the general shortage of dentists, it is quite plain that not enough of them want to make school dentistry a permanent career For this, the British Dental Association says, there are four main reasons (1) the attitude of the local authorities to the dental services, (2) their attitude to the professional staff, (3) the poor prospects of a career in local-authority service, and (4) the low and unrealistic salaries offered. The view taken by most local authorities that dental surgeons are primarily local-government officers, and only secondarily dentists, must deter many young practitioners The British Dental Association suggests that senior dental officers should be in full control of the dental services in their areas, and should no longer be subjected to the control either of doctors or of local-government officers More senior posts are needed, and salaries comparable to incomes in private practice, and with increments which do not cease after eight years' service, must be offered if the school dental service is to be saved from certain collapse

An independent report by Mr H R. Cullwick,[3] a Staffordshire dental surgeon, calls for the establishment of an autonomous school dental service, directly responsible to the Minister of Health He proposes—and his proposals are endorsed by some leading members of the dental profession—that the new service should treat children from 3 until school-leaving age Salaries for dental officers would start at £2000, increasing to £2300, senior dental surgeons would receive up to £5000 Money could be saved, Mr Cullwick suggests, by supplying all clinics from a central depot. For at least ten years the new service would cost more than the present one, and to offset this he proposes that adult patients, with certain exceptions, should pay the full cost of dentures

DIAGNOSIS OF MEDIASTINAL MASSES

IN the diagnosis of lesions of the mediastinum the first and most important step is to determine exactly where the lesion lies, since the type of lesion to be expected varies with the site in the mediastinum the predilection of neurogenic tumours for the upper two-thirds of the posterior mediastinum is well known.[4] Plain films, tomography, and screening are all useful in determining the site, and careful screening may yield further information, such as the presence or absence of pulsation and (with pleuropericardial cysts, for instance) the change in shape during respiration and Valsalva's manœuvre In addition the presence or absence of calcification can be determined, and the relation to the main pulmonary arteries may provide information as to whether some opacities are glandular. Most mediastinal lesions either displace other mediastinal structures into the lung field or carry the pleura in front of them, and nearly all present as a smoothly outlined opacity, it is only in the later cases of malignant neoplasms or in the presence of infection that this smooth outline is lost Again, evidence of rate of growth may indicate malignancy or infection, and, in lesions which are situated posteriorly, examination of the dorsal spine for bony destruction, infection, or enlargement of the foramina may prove of diagnostic value But commonly with lesions involving the upper middle and anterior mediastinum the inner border of the lesion cannot be demonstrated, and the outline of the lesion cannot be distinguished from the shadows of the great vessels by tomography, straight films, or screening Anomalously, aortic aneurysms are often still, whereas neighbouring cysts often appear pulsatile and sometimes apparently expansile

To differentiate between these lesions additional information is usually needed. Kincaid et al[5] have examined 200 such cases by contrast injection, either by angiocardiography or by direct thoracic aortography The patients had previously been investigated by other methods In half the cases the findings by fluoroscopy were indeterminate, and in a quarter frankly misleading Tomography and bronchoscopy similarly were of no definite diagnostic value, whereas contrast injection always revealed vascular lesions, such as aortic aneurysms, and confirmed that anterior mediastinal tumours were not aortic in origin In addition contrast examination proved helpful in planning the operative procedure, either by showing malignant invasion of the large vessels—particularly the superior vena cava—or by indicating the length of graft required when the vessels were involved by non-malignant lesions Of the 200 cases examined, 188 were subjected to the potentially safer investigation of angiocardiography and only 17 to direct thoracic aortography Kincaid et al recommend the use of either sodium diazotrizoate or methyl glucamine diazotrizoate, and, except for one case in which the medium was accidentally injected into the soft tissues of the antecubital fossa, no serious side-reactions were noted

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[1] See *Lancet*, Aug 13, 1960, p. 358

[2] Memorandum on the Local Authority Dental Services *Brit dent J* 1960, 109, 275 Reprints obtainable from the British Dental Association, 13, Hill Street, London, W 1

[3] See *Birmingham Post*, Oct. 4, 1960

[4] Curren, A. R. Gale, J W *Arch. Surg Chicago*, 1949 58, 797

[5] Kincaid, O W, Brandenburg, R. O, Bernatz, P E. *J Amer med Ass* 1960, 173, 613

GOVERNMENT BY APPOINTMENT

ONE of the social developments of recent years in this country has been the establishment, under State auspices, of public services administered largely by members of the public Previously government had vested almost entirely in two groups—politicians (national and local) elected by democratic franchise, and professional administrators recruited in accordance with rules designed not only to test their qualifications but also to avoid patronage The new services, however, have been largely entrusted to boards and committees whose members are neither politicians nor Civil Servants but are hand-picked for their task

Of this new system the National Health Service is perhaps the most striking illustration In England and Wales there are 15 regional hospital boards whose chairmen and members are appointed by the Minister of Health, and 382 hospital management committees appointed by the regional hospital boards, the boards of governors of the 36 teaching hospitals are also appointed by the Minister of Health In Scotland there is a similar pattern, the Secretary of State appoints 5 regional boards, and these in turn appoint 84 boards of management For the general-practitioner services each county and county borough (except in a few cases where there are amalgamations) has an executive council with subordinate committees, a fifth of the council members being appointed by the Minister Appeals against the decisions of the executive councils on matters of discipline go either to the Minister or to the National Health Service Tribunal—itself appointed by the Minister though the chairman is chosen by the Lord Chancellor

A broadsheet from P E P[1] suggests that the administration of public services through boards and committees now involves something like 40,000 posts at national, regional, and local level The use of appointed boards and committees in preference to the elected local authorities has come to stay—first, it is suggested, because of the need to secure people with particular qualities for particular jobs, and secondly because of the Minister's need to exercise some form of remote control

In considering the new arrangements, we should note that, though some boards comprise highly paid full-time members, most of the appointments in question are part-time and unpaid thus the boards and committees which do so much to administer the health services are almost entirely composed of part-time voluntary members Again, the appointment of some boards and committees may be preceded by a good deal of consultation As the P E P broadsheet points out, the Minister of Health, before appointing members to the regional hospital boards, consults universities, representative medical organisations, local health authorities, and other bodies such as hospital associations and trade unions, sometimes the chairman of the board is also consulted In appointing hospital management committees, the boards again consult various interested organisations—e g , trades councils, the Royal College of Nursing, hospital contributory schemes, women's institutes, the Red Cross, the St John Ambulance Brigade, the Women's Voluntary Service, and chambers of commerce Such consultation is of great value in providing names of possible candidates, and it also stimulates the interest of the bodies consulted But the Minister and the hospital boards are not limited to names put forward in this way, and the person appointed serves as an individual and not as the representative of any organisation

Apparently, however, consultation on this scale is not typical of the other public services For example, in appointing its tribunals, the National Assistance Board seems to rely almost entirely on the recommendations of its own local officials Lack of adequate consultation may be responsible for what P E P call "excessive plurality" in public offices, every member of the London County Council holding (it is said) an average of nearly six other public posts Some plurality is of course desirable, but there is strong evidence that too few people have too many appointments Possibly the number of people able and willing to undertake voluntary public service is not so great as might be supposed, or perhaps there is an official tendency to "play safe" and to appoint only known and trusted people

The P E P broadsheet is almost entirely devoted to the problem of how members should be appointed to boards and committees, but the development of the system raises larger questions that will someday have to be considered Is administration by appointed committees efficient? Are the most suitable persons found? Should the Government have such large powers of appointment? And is it true that Ministers have more control over appointed boards than over local authorities? As regards this last question, we should say that they probably have not, for Whitehall can and does control the activities of local councils in considerable detail In the health service the advantage to be claimed for "government by appointment" appears to be twofold First, it enables the service to be administered by mixed committees of laymen and doctors (We do not ourselves rate this advantage high, since we believe that medical influence can be exerted more effectively through strong advisory committees, as was usual in the voluntary hospitals) Secondly, the wide consultation undertaken by the Minister and the boards makes for the selection of laymen who may be more representative of the public whom they serve than elected councillors would be

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The Earl of LIMERICK has been reappointed a member of the Medical Research Council, and Mr E F COLLINGWOOD, SC D , appointed a member in succession to Sir Geoffrey Vickers Lord Limerick will serve as chairman and Dr Collingwood as treasurer Dr THEODORE CRAWFORD, professor of pathology in the University of London at St George's Hospital Medical School, and Dr W M MILLAR, Crombie-Ross professor of mental health in the University of Aberdeen, have been appointed members in succession to Prof G Payling Wright and Dr Denis Hill, who are retiring

Prof J M MUNRO KERR, emeritus regius professor of midwifery in the University of Glasgow, died at Canterbury on Oct 7, at the age of 91

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[1] Government by Appointment *Planning*, 1960 26, no 443 Published by Political and Economic Planning, Queen Anne's Gate Pp 19 3s 6d

Special Articles

PATHOLOGISTS AT THE CROSSROADS*

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AT the present time there is much very sincere, yet sorely troubled thinking about the future organisation of pathologists.

For the title of this address I use the words "at the crossroads" with full realisation that a crossroads is a place from which one can proceed in a variety of directions—onwards to a new destination, to right or to left, or just plain backwards. Before we can reach any valid conclusion about what course to pursue, we must try to understand the causes and the distribution of the present discontent among pathologists.

So far as I can ascertain, the unrest is chiefly on the part of the younger consultants in hospital pathology and those who have not yet reached that rank, but many of the more senior men, and some academic pathologists also, have engaged themselves in the matter actively because they are anxious to do everything in their power to ensure that the pathologist of the future shall be able to enjoy a professional career in the most favourable circumstances.

* * *

In thinking of the pathologist, whether at the crossroads or elsewhere, we must first take into account the nature of his work, and this seems to me to fall into two main classes. Pathology has been defined very generally as the study of disease by scientific methods, and it has two main purposes—namely (1) to advance fundamental knowledge of the nature of disease and of the mechanisms by which disease is produced, and (2) to apply existing knowledge to the diagnosis and prevention of disease with a view to facilitating treatment, even if the latter is not properly the concern of the pathologist in other than an advisory capacity. It may be that one of the causes of present discontent lies in the drift apart of these two functions, as Dible has stated, and we should inquire into the practice of clinical pathology in this country to see whether we can improve it and remove the causes of the disquiet.

The continued advance in technical methods has multiplied very greatly the demands upon the laboratory for routine tests, and there are few laboratories, if any, where the technical staff has grown in proportion. Several of our most distinguished colleagues have expressed anxiety on this score and deprecated the almost total submergence of the clinical pathologist in carrying out routine tests at the behest of the clinician—a position which may well induce a feeling of inferiority if the pathologist has no say or choice in the selection of the work he has to do, and allows himself to be used as one whose work is merely ancillary to that of the clinician. There is no single remedy for this overloading of existing resources, but as far as possible merely technical work should be allotted to technicians, so that the pathologist shall have more time to widen and advance his fundamental knowledge as an exponent of one of the basic sciences of medicine on which clinical work is founded.

The medical and technical staff of hospital departments has all too often been kept at so low a level that energies are wholly spent in getting through the day's work, and this is all the more true when the duties involve so-called emergency calls at night and at weekends, not all of which are real emergencies. The clinical pathologist could be protected by the senior clinician from exploitation of this kind, but such discrimination and care are less likely to be exercised on his behalf if the pathologist allows himself to be relegated to the position of a mere servant of the wards.

The volume of hospital work has increased by virtue of a law that antedates Parkinson—namely, that the successful research of today becomes the routine of tomorrow. It is not so long ago that the pathology department of the hospital was known as the research department, and it is part of our duty to see that the title shall continue to be worthily applied.

* * *

It is to the credit of pathology that it brought medicine freedom from the shackles of Galenic authoritarianism, and it is still true that research in the laboratory in one or other of the four branches of pathology is the chief source of the increase in scientific clinical knowledge that is so striking a feature of medicine today.

The first of its four constituent disciplines to develop was morbid anatomy, and the morbid anatomist and histologist was trained largely on the apprenticeship system, rather unsystematically, but with lots of room for individuality. Of all the divisions of hospital pathology, the diagnostic problems in morbid anatomy and histology are the most exacting and the most personal. There are no controls, there are no tables of biological reactions such as can be applied to bacteria, and there are no standard solutions such as the chemist uses to check his results and set his confidence limits. There is only the pathologist, the sections, and the microscope, and his experience to guide him.

Bacteriology was the second of our disciplines to evolve, and, although much of the routine hospital work can be carried to the reporting stage by the trained technicians, hospital bacteriology offers a rewarding field to the trained and inquiring mind in the tracing of outbreaks of infection and eradicating the causes, in ensuring sterility, in controlling cross-infections, and in understanding how and why bacteria come to cause disease, and how it can be cured or averted. In addition, more academic biological bacteriology is also open to those whose interests lie in that direction. I shall no more than mention virology—a younger relation of bacteriology but one rapidly going its own way. The interactions of bacteria and viruses present fundamental questions of which we have only begun to glimpse the answers.

Hæmatology is the discipline that has retained the closest connection with clinical medicine, and indeed it is still practised by physicians to such an extent that this division of clinical pathology sometimes operates more under the department of medicine than of pathology. Here too the rapidly advancing technology of the subject is tending to lead to greater specialisation, and I believe that general physicians are gradually handing over more and more of the routine investigation of all hæmatological problems to that division of clinical pathology. In view of the ever-increasing complexity of the blood-groups and of cross-matching techniques, of the progressive subdivision of the clotting factors into more and more fractions of clinical significance, and of the elaboration of techniques for the investigation of hæmolytic anæmias and of types of hæmoglobin, it is not surprising that the physician turns more and more to the professional laboratory worker. A certain amount of robot working by electronic machines has already been introduced and no doubt more is to come, but there is a large and expanding area in which expert knowledge is required and for which specialised training must be provided within the laboratory

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* From the presidential address to the Association of Clinical Pathologists on Sept. 30, 1960.

Our fourth subdivision, chemical pathology, presents special problems In it, as in bacteriology, a large part of the routine hospital work can be and is increasingly carried out by technicians and other workers not medically qualified In this field we have recently seen the first serious attempt to introduce automation, and it seems likely that robot analysis will become more popular in hospital departments where large numbers of simple repetitive tests have to be carried out for the control of clinical treatment Much of the routine chemical pathology of hospital departments can therefore be carried out by workers who are capable of following given directions and are able to assess the accuracy of their results by the use of standardised solutions as controls Like all simple repetitive work this is unlikely to hold the interest of a lively mind for long, but before the medical graduate can go further in chemical pathology he requires a greater basic knowledge of chemistry and of biochemistry Without a science degree, he needs further fundamental training, which it is almost impossible for him to receive while engaged in full-time hospital work The Association of Clinical Pathologists was able to persuade the Ministry of Health that aspirants to chemical pathology might be seconded at the registrar stage for a year of fundamental study in chemistry while receiving full pay It is hoped that this will enable the supply of would-be chemical pathologists to be increased, but it is as yet too early to know whether the scheme will succeed

* * *

We can lay down, therefore, a general pattern of development for the young pathologist in training—that he should be given the opportunity to acquire a certain foundation of experience in each of our four disciplines and thereafter take up whichever branch of work his inclinations and opportunities favour If during this time he can be given a problem to pursue, so much the better Every effort should be made to encourage this activity I am convinced that the hospital pathologist will be a better man and will do a better job in his daily routine if he succeeds in combining some research interest with his daily work as soon as he has mastered the initial rotational training I do not advocate that he should write for the sake of writing, but much valuable observational research remains to be done

What of the other side of pathology, the so-called academic side? Here teaching and research are the predominant interests and it is the duty of universities to foster them Where university and hospital appointments are combined, the professor, and especially his fairly senior staff, should not be so overburdened with routine hospital duties that their primary purpose is defeated Nowadays most professors are glad of a share of the routine as a happy relief from committee meetings and administration, but the lecturer staff can suffer badly unless they are protected by their terms of service

* * *

We have glanced briefly at the training that the young pathologist is likely to undergo nowadays At the end of it what has he got to show that he has successfully completed the round and had further experience in one or more fields? If he has stayed in an academic department and been fortunate in his research he will probably have an M D or other higher degree by presentation of a thesis on a selected topic But what of the man who has not been in a teaching department but has been busily engaged in hospital pathology for five years or more under a good group of consultants who have taken the trouble to supervise his training and experience? It appears that he feels a sense of frustration, and sees himself at a disadvantage as compared with his contemporaries in medicine and surgery, because they, after a comparable period of training are likely to have acquired the M R.C P or F R C S This feeling is likely to be intensified when he has attended a few appointment committees and had to explain why he has no higher qualification This sense of frustration is one of the most potent causes of unrest today

In what ways are pathologists made to feel that their position is regarded as inferior? Regarded by whom? Not by themselves, unless they have a guilt complex and feel that they occupy a position of equality that is undeserved Nor by the administrative authorities, for they have admitted equality in the only way they can, by awarding full consultant status and equal pay Nevertheless there is a substratum of truth to be uncovered

In the pre-N H S days there was a widespread custom in England, if not in Scotland, of regarding as ineligible for appointment to the medical staff committee of the hospital anyone in receipt of a salary, even part-time The non-academic pathologist, to survive at all, was necessarily in receipt of a salary because, in contrast with physicians and surgeons, he had only a very restricted scope for earning a living by private practice In many cases this meant that the pathologist was excluded from participation in hospital affairs on equal terms with his clinical colleagues because he was thought to have a vested interest This unwarranted prejudice has, I believe, left its mark on staff relationships to this day The pathologist's salary was usually part-time and his income had to be supplemented by private practice in clinical pathology, for which he was again dependent on his clinical colleagues

This continual carrying out of tests at another's bidding, and providing results to establish a clinical diagnosis for which the pathologist may receive little acknowledgment or credit, may have depressed some clinical pathologist's assessment of their own position I think this is false and unworthy, for if the clinical pathologist so hankers after ultimate responsibility for the care of the patient that he is unhappy without it, he is in the wrong section of the profession Having chosen his field of work he cannot reasonably grumble if it does not cover those parts of medical practice in which he finds his deepest interest If prejudice of that kind still survives, surely it must be dying out Physicians and surgeons, too, are now paid for their hospital services, either full time or part time, and their position is in no way different from our own

The other chief cause of dissatisfaction however is, worthy of more detailed inspection—namely, the lack of a specific higher qualification in pathology to testify to a general level of professional competence in the chosen subject

* * *

Higher qualifications in pathology have been under active debate in the Association of Clinical Pathologists since 1947 Many pathologists have expressed the desire for such an examination in the belief that successful completion would give them additional status, if only the examination could be universally recognised as of equal standing with the M R C P By *status* I understand them to mean that they are thereby acknowledged to belong to a professional organisation or society which is of high repute, and is therefore presumed to shed some of its lustre on them It is equally true, however, that the repute of a society depends on that of its constituent members, who by their professional activities determine the place that the society will be accorded by similar professional organisations and within the community

The comparison most frequently made is with the higher qualifications of the Royal College of Surgeons and the Royal College of Physicians, and so the demand is for something that will not be called merely a diploma, although of course all of them are diplomas The higher qualifications of these old-established corporations have attained their enviable position at least in part because of the difficulty in acquiring them, as is attested by a pass-rate of 10–15% Further it is now insisted by the colleges that the possession of these higher qualifications is not to be regarded as anything more than an indication of suitability to undergo further training in clinical medicine or surgery For this reason many have advocated that the M.R.C.P should be taken *before* embarking on a career in pathology, for its value as an indication of quality is beyond doubt

But is the M R C P the proper examination for a pathologist already in training? This is by no means universally accepted

The academic affairs committee of the Association was unanimously of the opinion that the M R.C P as it stands could not be regarded as a suitable qualification *in pathology* This implies no disrespect—the examination is not designed for that purpose Further, the evidence submitted to us left no doubt that, after a few years of enthusiastic encouragement of their juniors to go for the M.R.C P, many consultants in pathology had changed their point of view and were now convinced that this examination ought to be taken, if at all, *before* embarking on full-time laboratory training The reasons for this change of mind are not difficult to find The high-level clinical examination required of an intending physician is a serious problem for the man who has been working in the laboratory for a few years, for it requires not only the initial education of the senses but the maintenance of skill by constant practice I have on occasion suggested to clinical examiners that a distinction should be drawn between knowledge of medicine, combined with ability to interpret the history and physical signs, and the technical ability required to elicit and detect the physical signs This is, after all, the technical skill of the physician, and it is no more justifiable to demand it of the young pathologist than it would be to require the physician taking the M R.C P to perform personally all the laboratory tests thay he quotes so glibly So long as the M R.C.P examination remains in its present form—and there is no prospect of changing it—we must accept that it is not a higher qualification in pathology, however desirable it may be as an indication of general ability and suitability for specialist training Unless success comes quickly, the effort required to keep up the clinical skill is too great to make it a practical proposition while doing a full day's work in the laboratory Many heads of departments have had the painful experience of seeing a young man of adequate ability fail to pass at his first or second attempt and thereafter become virtually a passenger in the laboratory until this hurdle had been surmounted

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After the debate at Exeter in 1953, inquiry by the committee on training of clinical pathologists revealed grave dissatisfaction with the standard of would-be entrants into laboratory work It was surprising that at a time when promotion in the clinical field was slower and more difficult than ever, there should have been such lack of high-class recruitment into a specialty which was clearly going to expand and was likely to allow promotion to consultant status at an earlier age than in general medicine or surgery

The shortage of applicants was not universal I do not think it was experienced by all university departments, and at least we in Scotland had no real difficulty in maintaining the high academic standards to which our departments had been accustomed in pre-N H S days In this we were, I realise, in a privileged position, very different from that of some non-teaching hospital departments, which were inadequately staffed by technicians, insufficiently supplied with apparatus, and generally at the tail-end of any list of priorities for building or equipment In thus starving the laboratory service, and almost depriving the pathologists of hope that the rapidly mounting burden of routine work could ever be undertaken in reasonable conditions, the responsible authorities, whether central or local, did pathology a grave disservice and one that is not yet removed Recent graduates of high ability and promise were discouraged from entry to hospital pathology, and senior consultants in turn were depressed by their failure to attract men and women of the right type

At this time the cry was again raised that a material factor in influencing high-quality graduates to reject pathology as a career was the absence of a suitable higher qualification comparable to the M R.C P or F R C S In what ways then, apart from personal pride and satisfaction, does the absence of a higher qualification affect pathologists?

The Health Service Acts have rather elaborate machinery for the filling of all posts of senior-registrar status or higher In England and Wales representatives of the Royal Colleges sit on all committees for consultant and S H M O appointments, and in Scotland the procedure, although different in detail, is much the same in practice Thus it has come about that at committees for the appointment of a pathologist it is not uncommon for candidates who have no higher qualification of any kind to be asked to explain why this is so Indeed, even when the candidate has the M.D degree, sometimes it is suggested that this is not an adequate higher qualification because it may have been taken by thesis in a narrow and highly esoteric field of study that affords no guarantee of knowledge and experience in a wide professional field, however much it may indicate intrinsic intellectual ability

The standard exacted by the universities varies and their degrees are not strictly comparable Some confer only a pass degree, others award in addition two grades of honours and beyond that, for the highest class, a gold medal Furthermore, the circumstances under which a thesis is written must influence one's assessment of its merit, for the award of a pass degree to a candidate with all the resources of a university department behind him indicates a less meritorious performance than a similar award to a man working in a peripheral hospital laboratory with fewer facilities at his disposal Whatever may evolve, I hope that we shall never reach the position that there is only one portal of entry into hospital pathology through which all must pass by virtue of a specific examination This would, I fear, canalise the entry far too narrowly The academic departments are relatively few, but the opportunities they offer for scientific training are

6 The names of the three known peptide chains of human *hæmoglobin are α, β, and γ,*[8] *and it is* suggested that the normal chains should be designated in that way (i e , not α^A or α^F, β^A, and γ^F). The genetic superscript for the normal gene product + (α^+, β^+, γ^+) will not be used as it implies to the chemist a positive charge

7 The expressions β_4 for H and γ_4 for Bart's may be used when their identity is fully accepted However, until the next International Congress the traditional names should be mentioned at least once in each publication

8 The present custom to describe an abnormal chain by adding the name of the appropriate abnormal hæmoglobin in superscript should be *maintained* ($S-\alpha_2\beta^S_2$, $Hopkins-2 = \alpha_2 Hopkins-2\beta_2$)

9. A polypeptide chain should not be designated with a new small Greek letter (such as δ and ϵ) until chemical evidence for complete separate identity from the α, β, and γ chains (such as exists between these chains themselves) has been established, genetic differences notwithstanding

10 It is expected that the analysis of the aminoacid sequences in the globin molecule will eventually be followed by a precise chemical nomenclature Meanwhile if a hæmoglobin has been identified by the usual methods of electrophoresis, chromatography, spectroscopy, alkali denaturation, cold denaturation, and solubility tests, it should be described by the accepted capital letter as hitherto (S, C, D, G, E, &c) as recommended by the Working Party meeting at the sixth International Congress in Boston in 1956[9] If comparison has been made on the same lines and with the same completeness with a hæmoglobin carrying the name of a locality that *name should be applied If the abnormal chain is identified* this should be indicated by a subscript, (for example D_α, D_β) and until the full identity by examining the aminoacid sequences has been established this subscript should be followed by a declaration of origin ($D_{\beta\text{ Los Angeles}}$, $G_{\alpha\text{ Ibadan}}$) This implies that D_γ will have to be renamed $D_{\beta\text{ Punjab}}$ *If two or more of such hæmoglobins are then found identical* by analysis of the aminoacid sequences, only the name of the hæmoglobin which was first discovered and fully defined by the conventional methods should be retained For example, if $G_{\alpha\text{ Ibadan}}$ and $G_{\alpha\text{ Azuakoli}}$ are found to be identical regardless of which the aminoacid sequence has been fully examined first $G_{\alpha\text{ Ibadan}}$ should be the remaining name However, until the next International Congress the alternative names should be mentioned at least once in each publication

11 No generally acceptable name was agreed upon for the familial condition in which hæmoglobin F persists into adult age without morphological changes of the red cells and without anæmia The term non-microcythæmic thalassæmia was considered not specific enough as it might equally apply to the familial condition where hæmoglobin A_2 is raised without associated morphological changes If the expression " high F gene " is used this should be done with reservation and only provisionally until further knowledge allows better terminology

12 If several hæmoglobins are present the phenotype should be designated by listing the hæmoglobins in order of decreasing concentration regardless of genetical considerations (sickle-cell trait=AS, sickle-cell anæmia=SF, sickle-cell thalassæmia=SAF, or SFA, &c)

MEDICAL DEFENCE UNION

THE Union, which last week celebrated the 75th anniversary of its foundation, now has over 47,000 members, and membership is increasing by about 1000 a year

At the annual meeting on Oct 4, Dr S COCHRANE SHANKS, the president, said that, experience having shown that claims against dentists were usually less expensive than those against doctors, the council had decided to reduce the annual subscription for dental members from £3 to £2 The Union's overseas indemnity scheme had been extended to cover practitioners anywhere in the world except the U S A provided that they (1) had a qualification registrable with the General Medical Council or the General Dental Council, and (2) were on the register of the country in which they practised.

In 1959, 390 cases were referred to the Union's solicitors—a record number There were 106 cases of alleged professional negligence 11 were fought, and all but 1 were won Of the remainder, 64 were abandoned, and 31 were settled by a payment made or shared by the Union The same ratio as in previous years had been maintained—namely about 2 , 1 in favour of members In court cases the ratio was about 10 1 During the year 1 out of every 17 members had applied for assistance

Agreement had been reached between the three defence societies about the criteria to be satisfied when a member applied for assistance A member's name would now remain on the Union's register for six months after failure to pay his subscription on the due date Thereafter he would cease to enjoy the benefits of membership

In 1959 the Union had been called on to deal with no fewer than 20 cases arising from failure to remove a swab from a patient's body It had been decided in the courts that it was not sufficient for a surgeon to rely solely on the nurse's count but that he himself must take such additional precautions as were reasonable in the circumstances of the particular operation in order to minimise his dependence on the nurse's count It was hoped that teachers in surgery would draw attention to this fact

At a dinner held at Apothecaries' Hall on Oct. 4 to mark the 75th anniversary, the President responded to the toast of *The Medical Defence Union*, proposed by Sir Harry Hylton-Foster, Speaker of the House of Commons Sir Russell Brain proposed *The Guests*, and Sir David Campbell responded

Public Health

Smallpox

MODIFIED smallpox has been diagnosed in a Dutch businessman who arrived at London Airport on Oct 3 by flight BA 791 from Colombo, Ceylon This man attended the casualty department of Charing Cross Hospital on Oct 5, when he complained of an irritating skin eruption and was found to have a sparse rash He was admitted to Long Reach Hospital, Dartford

Those who travelled on the same flight as the patient have been traced Those known to have been in contact with him since his arrival in England include, besides members of the staff and some patients at Charing Cross Hospital, members of the staff and a few prisoners at Wormwood Scrubs Prison, which he visited on Oct 3

Infectious Diseases in England and Wales

Disease	Week ended September			
	3	10	17	24*
Diphtheria		2	2	3
Dysentery	351	2	310	134
Encephalitis				
Infective	3	2	4	
Postinfectious	2	1	2	1
Food-poisoning	197	215	196	210
Measles, excluding rubella	1398	1156	1093	1501
Meningococcal infection	10	11	16	20
Ophthalmia neonatorum	22	20	21	15
Paratyphoid fever	6	6	13	9
Pneumonia, primary or influenzal	105	122	126	139
Poliomyelitis				
Paralytic	9	5	13	3
Non paralytic	7	7	3	5
Puerperal pyrexia	181	178	127	158
Scarlet fever	169	166	210	275
Smallpox				,
Tuberculosis				
Respiratory	315	357	390	357
Meninges and C N S	2	5	2	9
Other	53	12	16	51
Typhoid fever	7	6	2	6
Whooping cough	1116	1376	1395	1132

* Not including late returns

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8 Schroeder, W A *Progr Chem org nat Prod* 1959, 17, 322
9 Lehmann, H *Blood*, 1957, 12, 90

Conferences

BURNS

THE first international congress on burns was held in Washington, D C, on Sept. 19–22 at the National Naval Medical Center, Bethesda. Prof CURTIS ARTZ acted as coordinator. Of the 150 taking part, about a quarter came from countries outside the U S.A. The members were welcomed by Dr FRANK BERRY, Assistant Secretary of Defense and honorary chairman of the congress, who recalled his own experience in the treatment of burns—local ice water, local ambrine, local coagulants, exposure, and now back to ice water The Surgeons-General of the Army, Navy, Air Force, and Public Health Service were also present.

There follow brief summaries of some of the contributions.

Dr OLIVER COPE (Boston) analysed 106 fatal burns in 1141 consecutive cases treated at the Massachusetts General Hospital. Improvement in the past decade was chiefly reflected in prolonged life, not in overall survival. Respiratory damage accounted for 50% of deaths, and local sepsis was the second commonest cause.

Dr NICHOLAS KETALIDES (Lima, Peru) reviewed the striking and well-known results obtained in Peru by use of oral saline in the treatment of burns shock. The results of saline alone seemed to be better than infusions with saline plus plasma, but the plasma therapy described would be considered inadequate by many people.

In a clear and carefully considered paper on sodium balance in burned children, Mr A. D R. BATCHELOR (Edinburgh) emphasised that during the early period of sodium retention considerable sodium loss could continue from the burn and reduce the positive balance of the first two days The later serum loss during the period of separation of sloughs would be enormous and was well recognised.

For eleven years the Richmond Burns Center have used dextran in the treatment of severe burns and are well satisfied with it, Dr B W. HAYNES, Jr (Richmond, Virginia), reported. There had been no hæmorrhagic complications, no anaphylaxis, and no increase of bleeding-time or clotting-time or change in prothrombin levels. Dextran seemed to restore cardiac output, as well as maintain circulatory volume.

A urologist, Dr J U. SCHLEGEL (New Orleans), made an interesting plea for the use of osmotic diuretics—e.g., 4% urea in 5% dextrose in water—to prevent renal shutdown. He emphasised the advantages of the bacteriostatic and bactericidal properties of urea in these patients

Dr FRANCIS MOORE (Boston) gave firm but qualified approval of 6% dextrose solution in the treatment of burns It now formed 25% of colloid administered. Dextran raised the glomerular filtration-rate which was the chief factor in urinary volume. It was the tubules which determined the quality of the urine. The dextran-treated patient exhibited "solute diuresis", and Dr. Moore believed that this was undoubtedly beneficial.

Dr H. A. FOZZARD (St. Louis) demonstrated that in experimental burns there was a true early cardiac insufficiency This fall in cardiac output could be prevented by dextran and [illegible] given together, but not by either separately

Dr A. MONSAINGEON (Paris) had studied tripeptidase activity in skin burns of intermediate depth, in the blister fluid, and in the plasma of both patients and rabbits Tripeptidase levels in blister fluid and in plasma were comparable, and they returned to normal after the slough separated. A rise in tripeptidase activity at the site indicated deep sloughing The method may help in therapeutic trials of anti-enzymes

Dr WILLIAM WARTMAN (Chicago) gave a detailed account of the postmortem findings in 41 patients dying of severe burns. They re-emphasised the importance of the pulmonary lesion and the multiple mechanism of death in most cases. 13 were classified as shock deaths, 5 were due to early gross lung changes, 16 to sepsis, 3 were attributed to gastrointestinal ulcers, and 1 to hepatitis

Dr F B HERSHEY (St. Louis) was interested in enzyme changes in the zone 2 (of Peters) and in the mechanism responsible for a 98% fall in oxygen uptake in skin exposed to 55°C for 60 seconds. He analysed the role of the Krebs cycle and of succinicdehydrogenase in these mechanisms

Dr T STENBERG and Dr K. E. HOGEMAN (Malmo, Sweden) reported studies with ^{131}I-tagged rose-bengal in burned rats Liver damage proportional to the extent of the burn was found, and was correlated with a decreased bile-flow Similar changes were also found in burned patients

The main impact of the papers on the first day was to emphasise the importance of pulmonary damage, and the need for tracheostomy in flame burns of the face, especially those incurred indoors The value and general acceptance of dextran as a plasma-expander, and as a corrector of decreased cardiac output in the early stages, were clear There was also general support for the use of solute diuresis by urea or mannitol in the prevention and treatment of early renal shutdown.

* * *

Dr S R. ROSENTHAL and others (Chicago) described evidence of the presence of toxins and antitoxins in the blood of burned animals and patients Extracts of burned human skin inhibited Hela tissue-culture growth. This work suggested the possibility of producing antisera to toxic products of burned skin.

Dr. N A. FEDOROV (Moscow) said there were changes in the antigenic structure of blood after burning. Specific auto-antigens appeared in the blood of animals and man, similar to those constantly found in burned skin. These antigens were found in blood within 6–24 hours of burning. The blood cells of burned patients had antigenic properties against antitoxin of burns, and a therapeutic serum had been prepared which had prolonged and preserved life.

Dr. M. DOBRKOVSKY (Prague) had been able to correlate antigenic and biochemical changes in burned skin at various stages Antibodies appeared between 4 and 8 days after injury

Discussing disturbance of protein equilibrium after severe burns, Dr T G BLOCKER and others (Texas) described dietetic needs, based on a study of 1000 burns and of the accelerated anabolism which ensued. 2·4 g. of protein and 45–90 cals per kg. per day was recommended, plus potassium by enteric-coated capsules The negative nitrogen balance was a matter of increased nitrogen turnover the unsolved question was what drives this mechanism.

Dr CARL MOYER (St. Louis), in an important study of vaporisation heat loss (V.H.L.), showed that this took place chiefly through blistered skin, but also through thick sloughs, and greatly accelerated the metabolic-rate. V.H.L. was more through skin than through lungs, and it could be checked by local cover, by immersion in a bath, or by use of a 'fog room" A strong warning was issued by Dr MOYER and Colonel E J PULASKI about the serious dangers of local abscesses and pyæmia when burns were covered by impermeable dressings It was far safer "to pile on the fuel" until we had safe methods of controlling metabolism rather than use immersion or impermeable dressings, such as 'Cellophane'

Dr W T TUMBUSCH, Dr E. H VOGEL, and others (Texas) pointed to the rising incidence of pseudomonas septicæmia after burns Of 740 patients, of whom 140 died, 63% had septicæmia, chiefly *Staph. pyogenes aureus* and pseudomonas, but with different clinical courses Pseudomonas septicæmias were fatal within 12–48 hours, with hypothermia, leucopenia, and hæmorrhage, and *Staph. aureus* produced pyrexia, mental deterioration, and leucocytosis. There was a 50% mortality with *Staph. aureus* and 100% with pseudomonas

Dr KETALIDES and others (Lima) presented the results of 3000 cultures to show that antibiotics were ineffective against invasion by *Staph. aureus* or pseudomonas, but that gamma-globulin prophylaxis plus antibiotics significantly reduced septicæmia and death in young children.

Dr S M Levenson and others (Washington) showed the decisive effect of previous sublethal total-body radiation (T B R) on resistance to the shock phase of burns This sensitivity was not specific to burns and extended to any trauma Any surgery could be fatal if performed between the 6th and 12th days of T B R

The highlight of the second day was the demonstration of a burns toxin and the possibility of producing an antitoxin If these hopes are realised the mortality of burns could be dramatically improved The work on vaporisation heat loss raises the prospect of eventual survival in 80–90% deep burns The limitations of antibiotic therapy in countering *Staph aureus* and pseudomonas invasion were underlined The wider use of gammaglobulins seemed justified

* * *

Mr A. B Wallace (Edinburgh) was anxious to see the formation of an international committee, under W H O auspices, to study means of preventing burns Dr Moyer said that there were 2 million burns a year in the U S A with about 8000 deaths

Mr Patrick Clarkson (London) illustrated mortality-rates in England and Wales in 1949–59 These remained constant at 600–700 a year despite some improvements in therapy and prevention, and a big increase in burns centres 20–25% were scalds, and 20–25% involved those under 15 years of age Long-term improvement in prevention could come only from new housing with safe heating and no open-hearth fires In London about 6 children per 150,000 under 15 were killed by burns per year In the major cities of the Midlands and the north of England, where open-hearth fires were commoner, 30–50 children per 150,000 under 15 years were fatally burned in a year Present fireguards were valuable but did not give complete security The open-hearth fire should go

* * *

At the Vyshnevsky Institute in Moscow burns shock was treated by pararenal block with procaine and by 1–3 litres of fresh blood or saline Only burns of less than 10% were treated by excision and primary repair, other burns had the slough excised at the end of the third week, and were resurfaced by patch grafts, not sheets Convalescent serum and corticotrophin were used for extensive burns with toxæmia

Dr J G Connell (New York) outlined successful rules of management for facial burns affecting trachea and lungs These included prompt tracheostomy, enzyme aerosol, and repeated suction plus oxygen

Mr D MacG Jackson (Birmingham) gave an authoritative account of primary excision and grafting—the most radical and logical, but potentially dangerous, treatment No reduction in mortality-rates or healing times had been effected The method may have advantages in expert hands for extensive burns involving fat, especially if they included the chest The method was, of course, an enormous tax on the patient and fraught with special dangers in inexperienced hands

Dr W A Altemeier (Cincinnati) pointed out the limitations of very early radical excision. 19 patients so treated had a 52% mortality, 35 comparable extensively burned patients treated along slower more conventional lines had a 51% mortality

Dr E J L Lowbury (Birmingham) recalled Colebrook's work demonstrating the effectiveness of local penicillin in protecting against injections of hæmolytic streptococci Prophylactic creams containing neomycin, polymyxin, and hibitane could be almost as effective in the elimination of local *Staph aureus* and pseudomonas infections, and the take of grafts improved significantly

The proceedings of the congress will become a standard work of reference on burns for a long time to come It was clear that the average standard of care to burned patients all over the world is vastly higher than it was ten years ago when the first symposium on burns was held in Washington The therapeutic problem today is the routine salvage of the 40%-and-over deep burn, most of whom still die The results are the same in most countries in the world A breakthrough in more than one position is awaited—safe, quick, reliable methods of removing dead tissues, and the provision of stored antigen and free skin, are still lacking Professor Artz has done a great service to this subject, and to all burned patients, in convening this congress

Patrick Clarkson

THROMBOSIS AND ANTICOAGULANT THERAPY

A symposium on this subject was held at Queen's College, Dundee, from Sept 28 to Oct 1

Dr J R A. Mitchell (Oxford) demolished many cherished concepts of coagulation and thrombosis Blood-clots and thrombi were entirely different in structure The former were composed of all the blood constituents deposited in a homogeneous fashion, whereas the latter contained selective depositions of fibrin and platelets Hence the demonstration in vitro of a factor which affected the one was no guide to its effect on the other Evidence also indicated that generalised atherosclerosis, coronary atherosclerosis, coronary thrombosis, and myocardial infarction were not closely correlated

Dr J C F Poole (Oxford) endorsed these views and described an in-vitro method of producing "thrombus-like" structures by rotating blood in a closed plastic tube. The thrombus had a "white head" composed of platelets and a "red tail" of red cells Heparin abolished the red tail, but not the white head, and the whole process was inhibited by short-chain fatty acids with upwards of 16 carbon atoms

Dr M Matter (Zurich) discussed the factors concerned in coagulation, and suggested that local changes in the vessel wall may be important

Prof H W Fullerton (Aberdeen), describing work on the recalcified clotting-time (R C T), stressed the need for meticulous technique He had found that a high-fat meal accelerated the R C T, this effect being prevented in healthy people by activity The acceleration was also prevented by phenindione in patients with either recent or long-standing myocardial infarcts

Dr S Niewiarowski read for Dr E Kowalski (Warsaw) a paper which showed that fibrinolytic factors and coagulation are interrelated For example, fibrinolytic agents not only digested fibrin but also inactivated factors V and VIII and released coagulation inhibitors

Dr A S Todd (Dundee) described an elegant method of placing tissue sections upon fibrin microfilms and observing the sites of fibrinolysis He found that these were concentrated around blood-vessels, fibrinolysis being most active in the endothelium of veins, notably after damage to the cells In thrombosed vessels fibrinolytic activity was localised at points at which the thrombus was not firmly attached

Laboratory Control of Anticoagulant Therapy

Dr H Hartert (Heidelberg), Dr W Zollinger (Zürich), and Dr W Walker (Dundee) described comparative studies of laboratory methods The consensus of opinion was that thrombotest has considerable advantages over other methods

Prof P A Owren (Oslo) said that in his view five categories of disorders deserved a high priority for long-term anticoagulant therapy These were rheumatic heart-disease with emboli, angina pectoris of less than two years' standing, myocardial infarction, atherosclerosis in the lower limbs, and intermittent cerebral ischæmia There were three groups of lesser priority —long-standing rheumatic heart-disease, angina pectoris of more than two years' duration, and repeated myocardial infarction

Clinical Indications for Anticoagulants

Prof R B Hunter (Dundee) described the evolution of the present position with regard to long-term use of these drugs in myocardial infarction, and Dr R L Richards (Glasgow) reported a prospective clinicopathological study which indicated that in patients who had received anticoagulant therapy

By this time I was making a name for myself, and when I bathed the head of a small boy who had fallen off a bus, my reputation was made Now sundry young ladies appear in my office with headaches, pimples, blisters, and splinters, and also ask my advice on halitosis, B O, and shallow irregular sleep One of our senior staff has shown me his psoriasis I have had to assemble a first-aid kit, and my stethoscope, newly cleaned and polished, lies on top Who knows, I might even get a chance to use it My wife treats me differently, too When I came home the other day with blood on my cuff, she gazed on me as she did years ago when, as a casualty officer, I regaled her with tales of horror and carnage Last week she even let me bandage little John's finger instead of taking him to a real doctor

* * *

My colleagues are always talking about their gardens, and I feel a bit out of it, since my own horticultural efforts have met with nothing but disaster I planted some melon seeds once, for example, on blotting-paper At first all was well They grew so fast, indeed, that I took to leaving the door of my flat open in the morning so that they could spread themselves into the hall if they felt so inclined, rather than lift the roof off It couldn't last, though One day they outgrew their strength, or perhaps used up whatever nourishment they had drawn from the blotting-paper, I should have mentioned that it was green blotting-paper Anyway, they lay down and died

Next I tried some cactus seeds I grew these strictly according to instructions, in a blue plastic tray of earth, and devoted much ingenuity to keeping them at a temperature of 70° After weeks of observation, they came up Unfortunately 25% of the crop was a weed, and 75% of the crop died.

My next experiment in propagation concerned an avocado pear I wasn't sure of the structure of this exotic nut, so I cut the first one open to see whether there were lots of little nuts inside There weren't, and, the price of avocado pears being what it is, I had to wait a year for another chance My second nut has been planted for several months now It hasn't actually sprouted yet

Perhaps I should try something simple next—like mustard and cress, or a carrot top I don't like to admit defeat though, especially since I read of a man who grows miniature Canadian redwood trees in pots

* * *

I was returning by air from one of our Hebridean islands after making preliminary arrangements for the visit of a mass-X-ray unit. From the armchair comfort of B E A I recalled with delight the tranquil pleasant way of life on that island and the charm of its people Someone at the meeting had—regrettably—suggested giving donated prizes to lucky numbers to encourage attendance at the X-ray sessions and the idea was taken up with acclaim When I left the story was sweeping the island that a tractor would be awarded to the thousandth person to be X-rayed The Fiery Cross could not have spread the tale faster and I neither confirmed nor denied it But I know that several bottles of whisky were donated, and it needed all my tact to decline an offer of 100 cigarettes as not being an entirely appropriate reward in this case

* * *

In desperation we decided to take active and drastic measures to improve the abysmal standard of behaviour of the younger generation An unyielding and consistent attack on the problem led to tears and bitter altercations, followed by, strangely enough, the playing of a gramophone, full blast through open doors

I used to regard record-playing as a harmless, if perhaps rather strange, outlet for aggression directed against the parents The children must know that it is now many years since we became totally immune to any amount of noise But now I understand the significance In times of stress and strife the record that is played is always the same On one side is a bouncing *My old man's a dustman* and on the other side is a mournful *Fings ain't wot they used to be*

Letters to the Editor

CHEMOTHERAPY IN CHRONIC BR

SIR,—The paper of Oct 1 by Dr P
colleagues is of great interest to us In 19
the Ministry of Pensions and National Serv
the names of people who had been certified
through bronchitis for more than a year in a
tinuously or for separate periods during the p

The Ministry's local officers kindly sent out
practitioners, as a result of which 91 patients w
us as outpatients Physical disability or n
prevented completion of investigation in 18 cas
presence of conditions even more disabling th
another 9 were excluded

The remaining 64 severe bronchitics include
given up work more than a year ago, and 6
worked for more than ten years They formed
as we had seen outside wards for the chronic si
disturbed Severely and continuously disable
suffered the acute exacerbations which had
punctuated their last working years 35 of the
were unable to walk 100 yards slowly on the le
rating, grade-5 dyspnœa) and another 15 were s
to be house-bound

Waxed closed cardboard containers stored in
department were used for the collection of sput
from these patients These specimens were te
select appropriate antibacterial drug treatment
creatin homogenisation [1, 2] the specimens were
blood-agar plates (aerobically and anaerobically
chocolate agar The cultures were examined at 24

We found that *Hæmophilus influenzæ* was isol
mens from only 7 cases, whereas in 27 colifor
were predominant, and 30 yielded *Streptococcu*
Many authorities are of the opinion that amon
H influenzæ alone or together with *Strep pneumo*
the aggravating organisms both in remission and
tion [3, 4] We were therefore surprised to find tha
of our severe bronchitics yielded growths of *H*
seldom and of coliform organisms so frequently

Nor did we find that, other than in 4 cases w
exacerbation, treatment with penicillin V or tetra
lines commonly recommended led to any signi
improvement

Our study leads us to suppose that an
bronchitics treated intermittently in the pa
were) with antibacterial drugs, there may
suppression of the usual bacterial flora, and
overgrowth of coliform organisms The
organisms which are relatively resistant to
treatment may also have contributed to
therapeutic response

The Royal Hospital,
Wolverhampton

J ASPIN
C H L

EXPERIMENTAL THYROIDITIS

SIR,—We were interested to read the artic
by Dr Shepherd and his colleagues T
demonstrate, as did those of the Buffalo wo
following intradermal inoculation of thyr
there is no close relation between the occ
autoantibody and of thyroiditis Our results,

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1 Rawlins, G A *Lancet*, 1953, ii, 638
2 Rawlins, G A *J med lab Tech* 1955, 13, 133
3 Mulder, J, Goslings, W R O, van der Plas, M C, Lop
Acta med scand 1952, 143, 32
4 May, J R *Lancet*, 1954, ii, 839
5 Terplan, K L, Witebsky, E, Rose, N R, Paine, J R
Amer J Path 1960, 36, 213

reported to the Pathological Society at Dublin in July, point to the same conclusion

Using a similar technique in guineapigs, but giving repeated injections of thyroid extract, we were able to produce unequivocal thyroiditis in all of 15 animals which were followed for more than 150 days, but the antibody titre could not be correlated with the degree of thyroiditis

There is now a good deal of evidence that the tanned-cell agglutinating antibody is not implicated in the causation of either experimental or human thyroiditis It seems more probable that the antibody and the thyroiditis stem independently from some other initiating factor as yet unknown, or alternatively that the antibody is a direct consequence of the presence of thyroiditis The latter suggestion would not be substantiated by the absence of antibody in the authors' experiment III, in which thyroiditis was produced by the injection of saline or adjuvant into one lobe of the thyroid Similarly, we have recently found that thyroiditis induced in guineapigs by radioactive iodine is not accompanied by production of tanned-cell agglutinating antibody

The parts played by the complement-fixing antibody, and by the cytotoxic factor described by Pulvertaft et al [6] and *Irvine,*[7] *are not yet clear*

It is difficult to understand why Dr Shepherd and his colleagues failed to produce thyroiditis with a single intradermal injection of thyroid extract, as it has already been shown that thyroiditis can occur as early as 2 months after one injection [5] Their suggestion that a simple saline extract of normal thyroid does not contain the required antigen is not borne out by either Witebsky's work or ours

Departments of Pathology and Clinical Pathology,
University of Manchester

G SCLARE
GEOFFREY TAYLOR

SIR,—The paper by Dr Shepherd and his colleagues describes the latest efforts to reproduce thyroiditis in rabbits artificially It would be interesting to know whether, and where, experiment-minded pathologists or clinicians are considering the mechanisms by which prolonged oral treatment with thyroid in human cases of the disease, produces the slow, but steady and striking, reduction in the size of the goitre so that eventually the thyroid gland may be almost or quite impalpable

Department of Pathology,
General Hospital,
West Hartlepool

R T COOKE

THE "COST" OF SEPSIS

SIR,—The report of Sept 24 from the Public Health Laboratory Service on the incidence of surgical wound infection was wisely cautious when estimating the monetary saving which would occur if postoperative sepsis were eliminated

The tentative calculations were based on the false assumption that hospital costs are 100% variable—that is, hospital expenditure varies directly with its use It is not surprising that the authors made this assumption, for it is made even in such authoritative economic analyses of the Health Service as the Guillebaud report [8] and *in the accompanying* publication by Dr Abel-Smith and Professor Titmuss [9]

The authors suggest that, if excess stay in hospital due to sepsis is 1,000,000 days per year, and if the average inpatient cost is £3 3 per day, then the annual monetary cost of sepsis is £3 3 million, and this could be saved by its elimination

These calculations indicate a failure to understand the significance of the figure, £3 3 per day The cost accountant produces it by dividing the total current expenditure of the hospitals (excluding those costs allocated to outpatient care) by the number of occupied beds However, as I indicated recently,[10] *nearly all hospital costs are overheads, or fixed, and* they continue whether a bed is occupied or not If sepsis is prevented, and a bed becomes empty, virtually no money is "saved" As the number of occupied beds (the denominator in the equation) has decreased, the only "monetary" effect is a rise in the inpatient cost per day! If the empty bed is used for a patient with some other disability, even this effect does not occur

I suggest that expenditure on medical care is not causally related to the prevalence of diseases It is usual to talk of the cost of sickness, cancer, &c., but this is only metaphorical There is *no expenditure on the abstraction "disease"—health* expenditure occurs when such concrete entities as nurses and dentists receive incomes The number of those providing medical care in a nation, and the size of their incomes, are determined by factors other than disease These conclusions, although they may conflict with conventional views, can be verified by observation.

Richmond, Surrey

J R SEALE

THE FEMALE PROSTATE

SIR,—"It is unfortunately still traditional for urinary symptoms in the female to lead to a gynæcological consultation " So writes Mr Thomas Moore,[11] and he is quoted with approval by Dr Herzl Kook (Oct 1) What exactly is this meant to convey? In my own hospitals I am glad to say that there is a free flow of patients in both directions between the urological and gynæcological departments, so that there is no backbiting between us

The relationships of gynæcologists and urologists are such that they each need the other at times There is no place for high-horse riding on the part of either of them

London, S E.21

PHILIP RHODES

THE VERY DEAF CHILD

SIR,—*May I comment on your annotation of Sept 17,* for I fear that some of the statements may mislead those readers who are not fully aware of the varying educational needs of children with impaired hearing?

Most teachers of the deaf do not regard as sacrosanct the definitions of the Board of Education's committee in 1938 Indeed, the National College of Teachers of the Deaf has been deeply concerned regarding the classification of deaf children, but teachers are aware of the difficulties in evolving a clearly defined system of classification which would meet the needs of all children In point of fact the 1938 system has rarely been rigidly applied, the terms grade 2b and 3 have largely been used in an educational sense, and improvements in auditory discrimination have been realised and recognised

You state that "non-auditory methods in special schools preserve the hearing loss of pupils unchanged" This shows a piteous ignorance of our schools Group hearing-aids were in use before the 1939–45 war, and in recent years a great deal of valuable auditory training equipment of all kinds has been supplied, and is being used by children with all degrees of hearing impairment

The last sentence of the article is jejune, and its implications are highly dangerous it disregards completely the vital need to consider the child as an individual How many children are, in fact, diagnosed "within the first few months of life"? What is meant by "adequate auditory stimuli"? Reference to the N C T D policy statement on the needs of the young deaf child will indicate the importance attached by teachers of the deaf to early diagnosis, parent guidance, and auditory training, but the selection of the most suitable educational environment is a complex and complicated *problem involving numerous* considerations in addition to hearing loss—powers of auditory *discrimination, mental capabilities,* lipreading abilities, communication skills, linguistic and emotional development, home background, and general educational attainments It is of

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Pulvertaft, R J V Doniach, D , Roitt, I M *Lancet* 1959 ii, 214

Irvine W J *J Endocrin* 1960 20 83

Cost of the National Health Service H M Stationery Office 1956

Abel Smith B Titmuss R M The Cost of the National Health Service in England and Wales Cambridge, 1956

10 Seale J R *Lancet*, Sept 24 1960 p 696

11 *Ibid 1960, i, 1305*

paramount importance that all these factors should be taken into consideration when determining a child's educational future

Longwill School,
Birmingham

H H SHORROCK
Headmaster

SIR,—Mr Gaskill (Oct 8) does not appear to have read very closely either your annotation of Sept 17 or the resolution from the Association of Non-Maintained Schools for the Deaf which is quoted in it "Grade III deaf children are being placed in *Units for Partially Hearing Children* (my italics), a move which is detrimental to the education of the severely deaf child"

Mr Gaskill ignores partially deaf units, each under the supervision of one or more teachers of the deaf, and concentrates entirely on the deaf child in the ordinary school Full discussion of this would be out of place here but it should be pointed out that Mr Gaskill betrays "a lamentable ignorance" of the auditory method, which depends, not on electronic apparatus, but on appreciating how the normal child learns to understand sound The importance of the attitude of mind is especially brought out in the work of Wedenberg, who prefers to start without electronic apparatus merely by speaking close to the child's ear [1]

I know of no-one who believes in merely placing the deaf child in an ordinary school "in the pious hope that by rubbing shoulders with hearing children they acquire speech automatically" Mr Gaskill should give chapter and verse for this statement, and should also notify the previous advisers of the alleged failures of the auditory method

Mr Owen (Oct 1) states that no-one has been able to formulate a classification with less defects and more practical advantages than that of the 1938 committee The following classification [2] is a very slight modification of the one I learnt from Mr Terence Cawthorne when I assisted him at the London County Council It has been used for many years at the audiology unit of the Royal National Throat, Nose and Ear Hospital

I Total Deafness
II Subtotal Deafness
    Hearing for sound only
    No discrimination between speech sounds
III Partial Deafness
    Hearing for speech sounds
    Ability to discriminate between
        (*a*) Vowels
        (*b*) Words
        (*c*) Sentences
(1) Partially deaf—severe
    Words heard at less than 3 feet
(2) Partially deaf—moderate
    Words heard at 3 feet or more hearing-aid required
(3) Partially deaf—slight
    Hearing-aid not required

The advantage of this classification is that it gives information about the distances at which sound, speech sounds, and speech can be heard It is a measurement of potential hearing—i e, hearing before it is trained The distance at which sounds and the voice are heard at initial testing gives an indication of the distance at which speech will be heard and understood once the child has learnt the meaning of the sounds he hears This learning process is fundamental to the auditory approach and until it is understood sweeping statements will continue to be made about the "failures" of the method The only "failures" of which I have personal knowledge of are due to neglect of the auditory approach at some point or other in the child's life

London, W 1

EDITH WHETNALL

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[1] Wedenberg E *Acta oto-laryng , Stockh* 1954, suppl 110
[2] Whetnall, E Proceedings of Vth International Congress of Otorhino-laryngology, 1953

SMOKING BY ADOLESCENTS

SIR,—May I endorse Dr Fisher's letter of Sept 24?

The time for kid gloves in dealing with this matter has gone, over twenty thousand deaths from lung cancer, a yearly sacrifice in this country, would, except for vested interests, compel instant action At what figure will the Government act? A hundred thousand?

This self-destructive habit can only be squashed in adolescents by adult example The other day I told a very young man that he was very likely planting the seeds of cancer of the lung, also of coronary disease and bronchitis, by smoking many cigarettes now and that they might foully blossom when he was forty He answered "Quite candidly I don't care a damn what happens to me when I am forty", the time of nemesis was too incredibly remote to deter him, that is as it should be, if a youth has long foresight and prudence there is something wrong with him.

It is the adults who stand indicted of mass murder by example From the physical side there is not a single thing to be said in favour of tobacco-smoking, and it is the adults' and especially the doctors' responsibility to save adolescents by example

Beckley, Rye

C G LEAROYD

ALL CYCLES ARE NOT MENSTRUAL

SIR,—Your leader of Oct 1 on cyclical œdema and shock, which discusses the interesting case reported at length by Clarkson and his colleagues,[1] follows them in a curious error which deserves a little discussion

They noted in their patient a "striking relationship of her shock episodes to the menstrual cycle", by which they mean that when she got an attack of œdema and vascular shock it was usually near the time of menstruation From this they concluded that the recurrent attacks were in some way caused by the menstrual cycle and should therefore cease if hysterectomy and bilateral oophorectomy were carried out Unfortunately the attacks recurred after the menopause produced by these operations, which thus experimentally disproved their hypothesis In spite of this, they cling in their discussion to the idea that menstruation "in some ill-defined way exerted a powerful modifying influence, unveiling an underlying disease process", and all the papers they seem to have consulted in the literature are concerned with aspects of menstruation

You follow them in this You and they seem to disregard the considerable literature which exists on cyclical recurrent physical and mental illnesses, even those with a cycle of about 28 days independent of the menstrual cycle Such illnesses are seen also in men, may continue into old age in both sexes, and when carefully recorded for a year or two in younger women can be seen running slightly and variably out of phase with the menstrual cycle Reimann [2] reviewed a number and described some of his own cases under the title of "periodic disease"—cyclic fever, œdema, arthralgia, and neutropenia (see his fig 1) Richter [3] likewise has collected many cases, while others [4,5] have made interesting steroid studies in their pathological analysis (see also Lingjaerde and Bredland's [6] fig 1)

Cyclic processes are facts of pathology as of physiology and multiple rhythms occur in the single individual throughout the evolutionary tree This knowledge does not seem to have penetrated clinical medicine in the way it has gained acceptance in the rest of biology, perhaps because so little is known of the underlying mechanisms of cyclic illnesses But at least a menstrual mechanism can usually be ruled out

In any event I think Dr Clarkson and his colleagues were guilty of rather careless thinking Their patient's attacks occurred up to 6 days *before* or 3 days *after* the onset of menstruation (in one instance 14 days after the onset), and as every endocrinologist knows *before* and *after* are two quite different biochemical situations it is not very likely that both could give rise to œdema and shock Surely we should expect a more precise time relationship than this between illness and menstruation, if we are to assume a physiological link and not just a coincidence

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[1] Clarkson, B , Thompson, D , Horwith, M , Luckey, E H *Amer J Med* 1960, 29, 193
[2] Reimann, H A *Medicine*, 1951, 30, 219
[3] Richter, C P *Recent Progr Hormone Res* 1957, 13, 105
[4] Hokfelt, B , Luft, R , Sekkanes, J *Acta endocr Copenhagen*, 1959, 32, 411
[5] Bondy, P K., Cohn, G L , Herrmann, W , Crispell, K R. *Yale J Biol Med* 1958, 30 395
[6] Lingjaerde, P , Bredland, R. *Acta psychiat , Kbh* 1954, 29, 355

One of the important positive findings of their work is, in fact, that the sexual cycle was not responsible for the regularly periodically recurrent illness If in the future we can avoid the hasty assumption that all cycles must be menstrual, more progress would be made in understanding and treating these curious cases

All Saints Hospital,
Birmingham
J L CRAMMER

*** In summarising the paper by Clarkson and others we noted the association with menstruation, but in our later comments we agreed with Dr Crammer that the fluid retention associated with menstruation could not have been the primary cause of this patient's œdema On the more general question of cyclical disorder, we referred to the paper of Rogers,[7] which brings together much evidence of a menstrual periodicity in various diseases — ED L

SIDE-EFFECTS OF LIBRIUM

SIR,—We have read with interest and concern the letter of Oct 1 by Dr Ingram and Dr Timbury We agree with their conclusion that this drug should be used with circumspection and scepticism, since we believe that this attitude should be adopted when any new psychopharmacological preparation is being investigated In addition to the report of Breitner,[8] which records improvement in all 7 cases of " obsessional states ", five other workers in this field have published interesting results

English[9] treated 87 patients with 'Librium' and states that he has found it to be effective in obsessive-compulsive disorders without producing excessive sedation Bowes,[10] in over 200 patients, finds this drug to be a significant advance in the treatment of anxiety states, and further, that it is effective in longstanding anxiety and phobic reactions and some obsessional states Tobin,[11] who was quoted by Dr Ingram and Dr Timbury on side-effects, stated in the same paper that of the 27 patients who exhibited obsessive thinking and compulsive behaviour, 23 derived some degree of subjective improvement Voelkel[12] claimed a favourable response in mild phobic reactions to a dose of 10–30 mg daily Garrone,[13] in a series of 180 psychiatric outpatients, reported a good response to librium in those patients with obsessional symptoms

In Dr Ingram and Dr Timbury's series of 15 cases of phobic anxiety states and obsessional neuroses, an improvement in 4 cases is considered disappointing and is of doubtful significance The corollary of this is that, apart from drowsiness in 7 out of 15 cases, the incidence of the other side-effects reported cannot be considered significant.

In our own experience with this drug in over 50 cases in psychiatric hospital patients and outpatients, the only side-effects occurring regularly are ataxia and drowsiness Ataxia generally develops after several days' treatment and usually with doses of 50 mg daily and upwards In outpatients this may be seriously inconvenient or dangerous In contrast, the drowsiness is often greatest in the first few days of treatment and may disappear without reduction of the dosage In degree it is similar to that with which we are already familiar when using phenothiazine compounds

Against this we have found the response to librium in obsessive-compulsive disorders and anxiety states to be distinctly encouraging, and we hope to publish results to substantiate this at a later date

Herrison Hospital,
Dorchester, Dorset
A G FULLERTON
M S BETHELL

SIR,—I wish to welcome Dr Ingram and Dr Timbury's suggestion that librium should be used with circumspection I have used this substance since April, 1960, in the treatment of 200 patients, and I am able to confirm its usefulness in the treatment of phobic and obsessional symptoms

The doses given to neurotic patients never exceeded 30 mg daily in divided doses As there is a tendency towards cumulative effects, this dose may be reduced after the first or second week The main side-effect seen in patients so treated was drowsiness None of the side-effects described by Dr Ingram and Dr Timbury were observed in my neurotic patients

In the treatment of psychotic or psychopathic patients larger doses are necessary, the maximum doses reached in such patients has been 150 mg a day In only 3 patients paradoxical side-effects like irritability and aggressiveness were observed

In the trial carried out at this hospital, librium has been found to be a valuable drug in the treatment of both neurotic and psychotic conditions, and side-effects can easily be avoided by observation of dosage recommended by the makers

Long Grove Hospital,
Epsom, Surrey
JOHN DENHAM

SIR,—Moved by the considerable public relations and advertising campaign, I decided to try using librium to allay anxiety in patients attending an N H S general dental practice

At first I thought the problem was a simple one of giving capsules to obviously frightened patients Thought convinced me that it is very difficult to assess a drug responsibly in the public forum, when so many factors other than the drug are at work

The attitude of the dental surgeon is important in reducing anxiety in dental patients A process of unconscious selection of patients by the dentist could operate Some practitioners may attract more very anxious patients than others The more obtuse of us may not notice that patients are anxious Most dentists must notice that variation in their own mood causes variation in the degree of apprehension shown by patients

Dentists also vary in their assessment of a drug according to their job A practitioner wants a drug that works with the minimum of inconvenience (cyclopropane is an excellent example of a drug that many dental practitioners dislike because of the protracted after-effects, yet its efficacy cannot be denied) On the other hand, a dental consultant needing to project a " brand " image of progress and advanced ideas might tend to ignore side-effects which do not matter much in a hospital

I felt it necessary to elaborate on this question of user bias since it is extremely difficult to assess whether librium has been effective in the circumstances in which I have used it

Out of 200 patients being treated at the time, I found only 15 whom I thought would benefit from librium 6 were children who resisted treatment.

Each child was given librium 1½–2 hours before the appointment (1 × 10 mg capsule) In 4 children, ages 4, 5, 6, and 8 years, the results were dramatic. Crying, fighting children became cheerful and cooperative. The 5th child did not respond The 6th child was a mental defective aged 8 years and did not respond to 2 × 10 mg 2 hours before the visit One child was tired and drowsy, obviously as a result of the librium

The main difficulty in summing up the effect of librium on children is that giving a child a drug may well relieve the tensions of a parent who anticipates a scene The resulting mood change in the parent then produces a cheerful child This makes the attribution of the cause of the child's good behaviour an uncertain matter

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[7] Rogers J *New Engl J Med* 1958, 259, 676
[8] Breitner, C *Dis Nerv Syst* 1960, 21 (suppl 3), 31
[9] English, D C *Curr therap Res* 1960 2, 88
[10] Bowes H A *Dis Nerv Syst* 1960, 21 (suppl 3), 20
[11] Tobin J M et al *Dis Nerv Syst* 1960 21 (suppl 3) 11
[12] Voelkel A Paper read at a Symposium held by the German Neuro-pharmacological Association Nürnberg April, 1960
[13] Garrone G et al Paper read at a Congress of Neuropsychiatry, Barcelona 1960

9 adults were given librium 3 were noticeably less apprehensive at their second visit The difficulty here is that many patients are much more agreeable at the second visit Patient and dentist have got to know each other a little, the lion has been bearded in his den (the patient's angle), and the fact that the patient has returned means to both a tacit admission of at least a degree of trust

I had one unexpected result To one patient I gave 3 × 10 mg capsules, 2 to be taken at 11 30 A M (for a 2 P M appointment) and 1 at 6 P M He slept for the succeeding 3 days, only getting up for meals However, he had lost quite a lot of blood, and I suspect had also taken a whisky or two (or three probably), and that this was a case of alcohol potentiation, though he would not admit that the responsibility for his stupor was his

The manufacturers' literature contained ample warning of side-effects, and a covering letter from the medical adviser contained a specific warning against alcohol potentiation and against driving after taking librium

Salisbury HUGH V CAPSTICK

SIR,—I read with interest the letter by Dr Ingram and Dr Timbury in which they reported results of treating 15 hospital outpatients with librium Their findings contrasted so strongly with my own experience of this drug that I felt impelled to describe the preliminary results with this drug in some of my own patients

Over the past three months I have used librium in a number of neurotic patients (25–30) seen in general practice, but up till now I have detailed notes and adequate follow-up observations on only 16 of them The conditions treated included anxiety depressions and other psychoneuroses, phobias, chronic alcoholism, and chronic depression, the main symptoms being anxiety, tension, and insomnia Some of these patients had been treated with a number of other drugs, without much success The usual dose was 10 mg three times daily, but doses of 60 mg daily were sometimes given The duration of treatment varied from ten to forty days

The results showed that 80% of these patients responded well, and symptoms were usually relieved within five to ten days In some cases, the effect of the drug was truly spectacular In 3 patients, it was possible to suspend treatment after seven days, without relapse

Regarding side-effects, the only ones complained of have been slight drowsiness (3 patients) and mild constipation (1) In none of them was it necessary to suspend treatment I have been so impressed with the effect of librium that I am now extending the present trial to include a larger series of patients and I shall hope to publish detailed findings later

It is likely, of course, that Dr Ingram and Dr Timbury's patients were more severely ill than mine and the higher doses used by them may have explained some of the side-effects they reported Nevertheless, it is hoped that my experience will encourage other general practitioners to try librium in the milder psychoneuroses so commonly met with in general practice

Leek, Staffordshire G KAGAN

SIR,—I have treated 15 patients with librium and only 2 have complained of side-effects Both were receiving 30 mg daily and complained of drowsiness In addition to drowsiness, one of these patients also complained of apathy These side-effects persisted in a reduced dose of 20 mg daily, and the drug was discontinued So far my impression is that librium is most useful in treating the moderate anxiety state with tension which is more commonly found in general practice

London, W 1 J B VERGANO

ASSESSMENT OF HEPATIC SIZE, SHAPE, AND CONTENT

SIR,—There may be others like me who are afraid to confess it, but may I state that I can rarely feel the normal liver through the abdominal wall? In view of the similar consistence of raw liver and steak, I am not surprised The palpability of the liver depends more on consistence than size As a control I have frequently got my surgical dressers at laparotomies to try to feel through the abdominal wall a normal liver which they have seen extending well below the costal margin, but they have never succeeded in doing so Is the frequency with which physicians state they can feel the normal liver merely an expression of their lack of opportunity of controlling their observations?

London, W 1 DAVID H PATEY

SIR,—Mr Grimshaw (Oct 8) rightly draws attention to the value of palpation at laparotomy as a means of avoiding a possibly useless resection of primary malignancy May I add a plea for an even simpler preliminary manœuvre? Laparoscopy, through a $^1/_2$ in incision under local anæsthesia, permits visual inspection of the liver surface, secondary deposits are unmistakable, and when seen will eliminate, by the same reasoning, the need for a major incision to admit the palpating hand This examination, performed as a routine in many centres on the Continent, often as an outpatient procedure, deserves to be more widely practised in Britain

London, W 1 BRIAN STANFORD

PERITONEAL SPLASH A PHYSICAL SIGN

SIR,—The letter of Sept 24 by Mr Lane Roberts was of considerable interest to me since an attempt to elicit the physical sign which he described in doubtful cases of perforated peptic ulcer has been used by me for many years I normally elicit this sign by grasping the pelvis on both sides and then rocking the patient gently from side to side Like Mr Lane Roberts I have found this sign of great help in differentiating between acute appendicitis and a perforated duodenal ulcer, but in spite of many attempts to elicit it in the conscious patient I have always failed Herein lies the limitation of peritoneal splash as a physical sign, one must await the arrival of the anæsthetised patient in the operating-theatre before it can be elicited Furthermore, only a positive result is of value, with a negative result doubt remains

University Department of Surgery,
The General Infirmary, Leeds F G SMIDDY

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P P /1

SIR,—The 10 patients treated with Dr Mooney and Dr Heathcote's vitamin-B_{12}/peptide complex are identical to those referred to in a previous letter

In 4 the dose was reduced to 20 µg In 2 of these patients (W R and S K), there was a recurrence of macrocytic anæmia, and in 1 (S K) signs of subacute combined degeneration developed A 3rd patient (A A) did not lose the feeling of fatigue and reach her highest hæmatocrit values until after being transferred to parenteral therapy Patients maintained on daily doses of 100 µg suffered no hæmatological relapse—only a decline of the serum-vitamin-levels—during the period of observation

The microbiological assay of serum-vitamin-B_{12} concentration is extremely useful as an objective estimate of the degree of vitamin-B_{12} deficiency [1] and we feel that cases of pernicious anæmia successfully treated should have serum levels within the normal range A decline to low levels is almost certainly the forerunner of a hæmatological relapse

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[1] Herbert, V The Megaloblastic Anæmias, p 82 London 1959

The object of Dr Mooney and Dr Heathcote's paper did not escape us, yet we felt it necessary to point out how important it is to check the serum levels of the vitamin whenever an oral preparation is used—especially when the doses recommended for maintenance therapy appear to be inadequate Finally it goes without saying that we do vitamin-B_{12} estimations as an accessory and not as a substitute for blood-counts

City General Hospital,
Sheffield

S VARADI

TROLLEY-SETTING

SIR,—May I give a further personal reassurance to Dr Behr (Sept 17) that an examiner of the General Nursing Council views with pleasure the advent of methods which will simplify the practice of aseptic technique, while making it safer for the patient

The introduction of a sterile supply service must certainly bring changes in nursing procedures The emphasis on the technical aspect of "trolley-setting" will disappear, I hope, and there will be more time and effort spent in learning the skilful practice of procedures

Relieved of the time-consuming chores of the older methods, the nurse should have more opportunity to develop the art of that nurse-patient relationship about which we talk so much and practise too little

The General Hospital,
Northampton.

MARGARET J COOPER
Principal Sister-Tutor

CHOLERA IN AFGHANISTAN

SIR,—You mention (Sept 3, p 544) "direct air communications" between Quetta (Pakistan) and Kandahar (Afghanistan) May I draw your kind attention to the fact that there is no direct air connection between these two towns, though both these border towns have airports? Kandahar is directly reached by air from Karachi, Teheran, or Kabul

Direct traffic between the two border towns goes by land a railroad leads from Quetta to New Chamam on the Pakistan side of the Khojak Pass, some 85 miles northwest from Quetta From Chamam to Kandahar the distance is 65 miles by good road

The most convenient entrance to Afghanistan from the East and by surface is through the Khyber Pass from Peshawar along a road which is motorable all year though bad in spots beyond Djelalabad inside Afghanistan

It is more likely that cholera spread by surface via the land routes from Pakistan to Afghanistan, especially since there is a continuous traffic of camel caravan in both directions throughout the year

F E PERABO
Karachi
W H O Senior Adviser

PROCHLORPERAZINE IN THE PROPHYLAXIS OF MIGRAINE

SIR,—Prochlorperazine ('Stemetil') is 1-(3-(2 chloro-10-phenothiazinyl)propyl)-4-methylpiperazine and belongs chemically to the phenothiazine group It was given to 54 patients with typical hereditary migraine and no other important diseases All were known to me because of earlier treatment, following the usual principles with differing results

1 tablet (5 mg) of prochlorperazine was given three times a day Patients with rare attacks have been under observation longer than those with more frequent ones in order to obtain a reasonable judgment of the prophylactic effect of the drug Observation time varies from one to four months

A "good" result (practically total relief of symptoms) was achieved in 17 cases and "improvement" (a substantial reduction of symptoms) in another 17 The remaining 20 were unchanged In treatment with placebos I have achieved a "good" result plus "improvement" in 25% of a similar group of patients

With prochlorperazine 2 patients complained of a certain apathy and another had a rash

Frederiksberg Hospital,
Copenhagen.

T DALSGAARD-NIELSEN

FATAL RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

SIR,—Dr Pryer and his colleagues omit the most pertinent comment in their report of Oct 1 This in my opinion should be a condemnation of the almost universal and unnecessary habit of inflating the cuff of endotracheal tubes in ordinary cold-list cases Even when respiration has to be assisted, a no 9 tube fits so snugly into a woman's trachea that the small leak acts as an accessory expiratory valve

St Bartholomew's Hospital,
Rochester, Kent

P AZZOPARDI

Obituary

THOMAS BAILLIE JOHNSTON

C B E, M D Edin

RENOWNED as anatomist and medical administrator, Prof T B Johnston was associated for nearly thirty years with Guy's Hospital and its medical school His prodigious services, first as dean of the school and then as superintendent of the hospital, stamped his own mark of quality on the character and work of both institutions He edited *Gray's Anatomy* from 1928 to 1958

Born in 1883, he qualified, like many fine anatomists, in Edinburgh—in 1906, with first-class honours He was demonstrator and lecturer in anatomy in Edinburgh until 1914, when he was appointed to a lectureship at University College, London He served in France and Italy in the R A M C during the 1914–18 war and was mentioned in despatches Then in 1919 began his long association with Guy's when he was appointed to the University of London chair of anatomy His executive skill was outstanding, and so rapidly did he win the esteem of new colleagues that only a year later he became dean of the medical school

Vandyck

His success at this difficult time, when the number of students was greater than it had ever been, was the first of many in a memorable deanship The trials of the early days are recalled by J J C

"When Johnston first came to Guy's the medical school buildings were quite inadequate for a large undergraduate teaching school The only funds available were students' fees and a small endowment income The anatomy department was in a ramshackle single-storey building of uncertain age, which might have been suitable as a store-room or a large public lavatory but certainly not as an anatomy department. The department of pathology and the postmortem room were in a converted warehouse widely separated from the wards, outpatients, and medical school And no long-term policy had ever been devised for the school

"Johnston early saw that much had to be done, but in the conservative atmosphere of Guy's progress had to be by infiltration rather than frontal attack. Fortunately he had qualities which quickly dispersed suspicions that a stranger from north of the Tweed might have aroused His broad vision and quick appreciation of problems, his well-balanced judgment and friendly attitude, enabled him to complete his plans relatively quickly A few years after his appointment a new anatomy department was built, and soon a new constitution, drawn up by Johnston, was adopted for the medical and dental schools and has proved its value over the years Some ten years later a new pathology department, amply provided for teaching and research, was opened Few of the present generation realise how much Guy's owes to his drive and vision "

In 1938 Johnston took on the new role of superintendent, at the urgent entreaty of the governors and particularly of his friend, Lord Nuffield, treasurer of the hospital Again he faced troubles, and J J C continues

" The financial situation in 1938 had reached a crisis when any day there might be no money in the till to pay the hospital staff Both officially and unofficially, Johnston tried all he could to get help from the London County Council and the Ministry of Health, but it was in fact the disaster of the war in 1939 and the formation of the Emergency Medical Service that retrieved the situation Johnston was appointed group officer for sector X, a post which he held until the end of the war In his headquarters, a large and cold Victorian house near Orpington Hospital, he had to perfect the organisation for dealing with casualties, and he was also responsible for the posting of medical personnel to the various sector hospitals, a difficult and invidious task He worked during bombardment from the air, slept in dugouts, watched the Battle of Britain, and arranged the disposal of wounded from Dunkirk

" After the war he returned to Guy's as superintendent Much work awaited him all the wards in Guy's House had been empty since 1939 and there was heavy damage from fire and bombs After two busy years, he retired just before the start of the National Health Service

" He was a bachelor and for long lived in or near Guy's He entertained a great deal and his hospitality was famous, for he was a perfect host, who planned every detail for his guests' enjoyment In his younger days and well into middle life he was a keen player of squash and lawn tennis For nearly forty years he was a member of Huntercombe Golf Club, where he quickly won the close friendship and respect of Lord Nuffield, whose many generous benefactions to Guy's were probably to some extent inspired by his confidence in ' the Dean ' "

Of his work as an anatomist, D V D writes

" Despite ever-increasing administrative duties, Johnston's interest in antomy never waned He was a keen member of the Anatomical Society and published several papers in the *Journal*, mainly on embryological topics He was, with his old friend, T B Layton, the second oldest member of the society He became vice-president and, after his retirement, was elected a life member He was a British delegate to the International Congress of Anatomists, in Milan in 1936 With A F Dixon and E B Jamieson, he presented to the society in 1933 the revised anatomical terminology, now known as the Birmingham Revision This was to be submitted to an International Congress of Anatomists but the opportunity did not come until 1950 when Johnston, with G A G Mitchell, was appointed secretary of the International Anatomical Nomenclature Committee which reported in 1955 The whole process took over twenty years and to it Johnston devoted much time and hard work He lived to see the new terminology adopted and even incorporated in his own works He resigned from the standing subcommittee only about a year ago

" In anatomy Johnston was best known as editor of *Gray's Anatomy*, a task which brought him contacts with medical men the world over About 1928 F G Parsons, of St Thomas's, was consulted by Longmans Green about an editor for Gray, to work with and succeed R Howden Parsons suggested Johnston, who met Howden on one of the latter's visits to the General Medical Council The meeting did not go well and ended in Howden resigning from the editorship, leaving Johnston to take on the job Like most Edinburgh men, Johnston had been brought up on Cunningham, and had never read Gray In the next two years, however, he revised it and entirely rewrote the section on embryology, which remains as an example of the precision and clarity of his work. He edited Gray for ten editions and held the reins until the centenary edition of 1958 For several editions he managed on his own, but later had the assistance of James Whillis and Frances Davies, each of whom in turn joined him in the editorship I joined them on the tragic death of Whillis and was soon to learn how kind and helpful T B could be, while paying meticulous care to every detail I shall always be grateful for the careful, considerate, and methodical training he gave me For T B nothing but the best effort and work was adequate for Gray

" His *Synopsis of Regional Anatomy*, first published in 1921 when he was at the height of his powers as a teacher, has also served generations of students Its latest edition, the eighth, appeared in 1957, nearly ten years after his retirement from the chair—adequate testimony to its quality and usefulness

" We mourn the passing of another of the great gentlemen of anatomy, but his name will live in the pages of the book he came to love so well "

JOHN TYRER JOHNSON

DSO, MD, B Hy Durh, DPH

Colonel John Tyrer Johnson died at Wooler, Northumberland, on Oct 5, aged 82

He was born at Newcastle upon Tyne and qualified with honours at Durham University in 1899 He volunteered for service in South Africa and later obtained a permanent commission in the RAMC He served in Korea in 1903 and in China during the Boxer Rebellion During the *1914–18* war he was awarded the DSO in Gallipoli, where he was the DADH, and also won the Order of St Sava of Serbia After the war he became successively ADH at Aldershot, ADMS Meerut District, Senior Medical Officer, Gibraltar, and finally DDMS, Egypt and Palestine Command

After his retirement from the Army Medical Services in 1933 he went into general practice in Guildford and later became deputy medical officer of health (casualty services) in Guildford just before the outbreak of the last war When the war began he rejoined the RAMC as a lieut-colonel and served throughout the war as senior medical officer of the Royal Arsenal, Woolwich For some years afterwards he was chairman of pensions appeals tribunals and travelled all over the British Isles

For the last ten years he had been enjoying a happy retirement in Scotland, and he returned to his native Northumberland only a few weeks before he died Tyrer Johnson is survived by his second wife and his daughter by his first marriage

ARNOLD AUBREY WATERMAN

B.A Cantab, MRCS

Dr Aubrey Waterman died at St James' Hospital, Balham, on Sept. 22 at the age of 42

He came to England from Trinidad during the war and studied at Cambridge and at Guy's Hospital After qualifying in 1951 he held a number of hospital appointments, including a medical registrarship at the National Temperance Hospital, before settling in general practice in Tooting D McW writes

" Aubrey Waterman was eminently suited both by training and temperament for general practice, for he had treated the sick of every colour and social class for a wide variety of illnesses He treated them all with unfailing thoroughness and compassion, and they soon found themselves at ease with one whose gentleness contrasted strikingly with a powerful physique and strength of will He was dedicated to his work but far from pompous about it His humour was ready and often ribald, and his devotion to medicine was almost equalled by his passion for music In this, too, he was devoid of intellectual pride and he was thus able to share his enthusiasm with less knowledgeable friends "

Dr Waterman leaves a widow

Notes and News

TOWARDS CLEANER AIR

INDUSTRY was praised for its efforts to reduce air pollution in a presidential address by Sir Hugh Beaver to the Clean Air Conference held in Harrogate on Oct 5–7 by the National Society for Clean Air Industry, Sir Hugh said, had already spent or allocated several million pounds for clean air measures As regards domestic smoke, heating appliances which could safely use many of our raw coals without nuisance and without skilled, or at least without skilful, and continuous attention had not yet been developed. "So if we believe in clean air, if we believe that too long have we subjected ourselves and our children and our aged to the unquestioned and lethal dangers of foul air, we must accept that there must in due course be some control over all domestic firing appliances wherever people are thickly congregated, or over the fuel used—or both." In industry it was possible to use in nearly all boilers and furnaces the poorest of coals so as reasonably to fall within the Clean Air Act. With the domestic hearth this was not so, and probably never could be so At a later session Mr F P Williams declared that nowadays almost all the smoke came from domestic fires, and that the observed pollution was not connected with the size of the town pollution was a much more local matter than had previously been thought. Mr E M Birtwhistle remarked that smoke issuing from a chimney was money being thrown away "smoke and inefficiency are great companions"

BOARD OF CONTROL

THE Board of Control, the central Government department which with the Minister of Health shares the responsibilities for mentally disordered patients, is to be dissolved in November under the provisions of the Mental Health Act, 1959 It was set up under the Mental Deficiency Act, 1913, and took over the functions under the Lunacy Acts previously performed by the Lunacy Commissioners Since the National Health Service came into being the Board has been responsible, broadly speaking, for matters affecting individual patients and the procedures applied to them, especially the procedures which authorise detention Some of these functions will in future be carried out by the Minister of Health and the hospital and local health authorities, while others will be discharged by the mental health review tribunals set up under the new Act.

In its last report,[1] the Board notes the encouraging trend in admissions on a voluntary basis In 88% of all direct admissions for treatment in 1959, compulsory powers were not used. This proportion included 16,724 patients (17%) received for treatment on an informal basis during the last three months of the year under the first commencement order made under the new Act. The Board is hopeful that this long-established trend will continue.

ELDERLY FEET

SINCE 1955 the National Corporation for the Care of Old People have been offering voluntary committees grants for chiropody services in exchange for records of such practical items as numbers of patients and treatments and cost. Their foresight has been justified, for last year the Minister of Health empowered local health authorities to set up chiropody services, and the corporation are now able to provide some practical advice[2] based on their barter of grants for records

They admit frankly that they are disappointed that the new powers given to the authorities are only permissive. They fear that, because of shortage of staff and the block grant, many authorities will hesitate to use them Those that do will probably run their service from their own clinics, though they may if they wish subsidise voluntary schemes In the corporation's view in many districts this second arrangement would have much to commend it. Where there is a shortage of chiropodists and where there are opportunities for private practice, a clinic-based service with modest sessional rates or full-time salaries is unlikely to attract many chiropodists But some might be willing to accept N H S patients if they were allowed to treat them in their own surgeries

Among other points which the corporation put forward for consideration is the decision where a patient should be treated. Many clinics, and some private surgeries, are not on the ground floor Some are not easily accessible by public transport. The elderly patient in need of chiropody is usually neither agile nor very mobile An awkward staircase or an awkward bus journey may prove an insuperable barrier to treatment. Indeed, in some country areas an adequate service can probably be provided only by domiciliary visits

The corporation are not able to offer firm estimates about costs to guide the organisers of official services, for many chiropodists reduced their charges for the voluntary schemes taking part in the survey Clearly an adequate chiropody service is going to add considerably to local-authority expenditure, but the corporation are convinced that it is a necessity for many elderly people and might lessen their demand on other health and welfare services—"painful feet leading to inability to get about easily may well prove to be the beginning of physical deterioration" This opinion is backed by Dr A N Exton-Smith's assessment of the value of chiropody to 120 elderly patients whom he examined. According to his survey (published as an appendix to the report). to all the patients it had proved of "great benefit as regards physical comfort, the maintenance of mobility, and improvement in morale"

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[1] Annual Report for the year 1959 of the Board of Control to the Lord Chancellor H.M. Stationery Office. 1960 9d

[2] Chiropody for the Elderly a three-year study of 120 voluntary schemes 1960 Pp 44 2s (From the Corporation, Nuffield Lodge Regent's Park, London, N W 1)

University of London

At recent examinations for the D.C.P the following were successful

E. C. Christian, J L. Grech, Bodh Krishna Jha, H. J Koornhof, H. G McDonald, J B MacGillivray, Rohina Newman W H Payne, M. J Phillips, Mohammed Qudratullah, Said Mohamad Sadique, Julian Shapiro, Ijemwa Osita Kanayo Udeozo, Dona Priyalatha Wijesinghe, Kishwar Zahur-Ud-Din.

Royal College of Obstetricians and Gynæcologists

Mr Ian MacGillivray will give a William Blair-Bell lecture on Friday, Oct. 28, at 5 P.M, at the college, 27, Sussex Place, Regent's Park, London, N W 1 He will speak on hypertension in pregnancy and its consequences

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty on Oct. 3, with Mr Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship

J H. Dagg, *qua physician*, Padma Pannala Reddy, N V Sweeney, *qua surgeon*.

Ciba Foundation Lectures

Prof J Konorski, of the Nencki Institute of Experimental Biology of Warsaw, will give a lecture on Friday, Nov 4, at 5 P.M., at the Royal Institute of British Architects, 66, Portland Place, London, W 1 His subject will be changing concepts concerning physiological mechanisms of animal motor behaviour Dr P J Thung, of Antonie van Leeuwenhoek-Huis of Amsterdam, will give a lecture on Thursday, Nov 24, at 5 P.M, at the Medical School, Edgbaston, Birmingham He will speak on ageing in the gonad-adrenal system.

Tropical Medicine Research Board

As announced in their last annual report, the Medical Research Council are setting up a Tropical Medicine Research Board to advise them on the promotion and coordination of all research in this field. The membership of the board, which has been decided after consultation with the Colonial Office and Commonwealth Relations Office, is as follows

Sir Harold Himsworth (chairman), Prof A C Frazer (vice-chairman), Sir John Boyd, Prof P C C Garnham, Prof W E Kershaw, Dr Raymond Lewthwaite, Prof George Macdonald, Prof B G Maegraith, Prof B S Platt, Prof M L Rosenheim, Mr H J Seddon, Prof E T C Spooner, Prof A W Woodruff, and Dr B S Lush (secretary)

The Chief Medical Officer and the head of the research department of the Colonial Office have been appointed assessors, and two assessors have been nominated by the Secretary of State for Commonwealth Relations

University College, London

Mr A F Huxley, F R S., will give his inaugural lecture as Jodrell professor of physiology on Tuesday, Nov 29, at 5 30 P M, at the college, Gower Street, W C 1. His subject will be theories of muscular contraction.

International Congress on Keratoplasty

This congress is being held in Prague from Oct. 19 to 21 The speakers from this country will be Sir Tudor Thomas and Sir Benjamin Rycroft

Prof Ruth Bowden has been elected chairman of the council of the Chartered Society of Physiotherapy in succession to Sir Harold Boldero, who is retiring after having served for six years

Mr Austin Concanon and Dr R E Angel are visiting Barcelona and Madrid from Nov 14 to 21 at the invitation of the Asociacion de Obstetricia y Ginecologia of Barcelona, and Prof J Botella of the Institute of Obstetrics and Gynæcology in Madrid

A meeting of the Biochemical Society will be held on Saturday, Oct 22, at 10 25 A M, at the National Institute for Medical Research, The Ridgeway, Mill Hill, London, N W 7

At the Midland Centre for Neurosurgery, Holly Lane, Smethwick, on Oct 27 at 8 P M, Dr Gunnar Brante of Eskilstuna, Sweden, will give a lecture on some aspects of the composition of nervous tissue and its alteration in disease

The annual dinner of the Society for the Study of Addiction is to be held at the Rembrandt rooms, Thurloe Place, London, S W 7, on Oct 17, at 7 30 P M The chief guest will be Mr A Dickson Wright Tickets (25*s.*) may be had from Dr Ellis Stungo, 93, Harley Street, W 1

Helping the Elderly to Live at Home —In this booklet Dr Kenneth Hazel, consultant gerontologist to Wolverhampton and Walsall, gives some useful hints to relatives or neighbours who are looking after an old person in his own home Copies (2*s*, postage 4*d*) may be had from the Central Council for Health Education, Tavistock House North, London, W C 1

Appointments

BARRY, J V, M D deputy director (S H M O), Glasgow and West of Scotland transfusion region, with headquarters at Law Hospital, Carluke
ENOCH, M D, M R C S, D P M S H M O, Runwell Hospital, Wickford
EVANS, AUDREY TREVOR, M R C S, D P H M O, London County Council
ISAAC, R G, M R C S M O, London County Council
LOCKHART-MUMMERY, H E, M D, M CHIR Cantab, F R C S surgeon, St Thomas's Hospital, London
MACARA, A W, M B Glasg, D P H assistant M O, school health and maternal and child welfare services, Bristol
SHERBROOM, D J, M B Lond, D P H deputy M O H, Kensington, London
WATKINSON, GEOFFREY, M D Lond, M R C P part time consultant in general medicine, York area

The Hospital for Sick Children, Great Ormond Street, London:

ABERDEEN, BOIN, M B Melb, F R C S, D C H surgical first assistant to the cardio thoracic unit
DINGLE, H R, B M Oxon resident anæsthetic registrar, Tadworth
FERRY, ANNA A, M B Sydney: house physician
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LOWE, J W, M B Leeds house surgeon
SARKAR, SATYABRATA, M B Calcutta, D L O senior E N T registrar
SCOTT, K H, M D house-physician
SHEVILLE, ELI, M B Glasg, D M R D: registrar in radiology
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ARKLE, J K, M B Durh, D P M senior assistant psychiatrist, Pastures Hospital, Mickleover, near Derby
SEARS, R T, M B Cantab, F R C S, M R C O G part time consultant obstetrician and gynæcologist, Nottingham and Mansfield area hospitals

Diary of the Week

OCT 16 TO 22

Monday, 17th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C.2
5 P M Dr A R Currie Modern Aspects of Thyroid Pathology
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr John Marshall Present Status of Therapy in Cerebrovascular Disease

Tuesday, 18th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
3 P M Sir Francis Fraser Challenge to the Medical Profession (Harveian oration)
ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M (Wright Fleming Institute) Dr Gordon Mitchell Heggs Pruritus vulvae
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Dr G A D Gordon Stereotaxis
ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P M Dr J D S Cameron Aspects of Hepatic Disease
SOCIETY FOR THE STUDY OF ADDICTION
8 P M (11, Chandos Street, W 1) Dr Abraham Walker (Lexington, Kentucky) Nature of Addiction and Habituation
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Dr J D Spillane New Dimensions in Neurology

Wednesday, 19th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 P M *Comparative Medicine* Dr J M Alston Recent Developments in Leptospirosis (Presidential address)
8 15 P M *General Practice* Dr R J F H Pinsent Art and Science in General Practice (Valedictory address)
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr Kenneth Lowe Tests of Renal Function
ROYAL FREE HOSPITAL, Gray's Inn Road, W C 1
5 15 P M Dr L N Katz (Chicago) Recent Advances in the Management of Atherosclerosis
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W 1
5 P M Dr W A R Thomson Doctors, Drugs, and Diseases (Bengué lecture)
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr Arthur Tickner Biochemistry of Skin Diseases
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr V H Springett Tuberculosis Epidemiology and Methods of Control
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W 1
8 15 P M Dr John Marshall, Dr R A Beaver, Dr J B L Howell Symposium on Management of Respiratory Emergencies
MIDLAND MEDICAL SOCIETY
8 15 P M (Birmingham Medical Institute, 36, Harborne Road, Edgbaston) Prof M Stacey Alchemy—Ancient and Modern
UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Mr Herbert Agar Irregular Bleeding at Climacteric
6 P M Mr G W Theobald Significance of Antenatal Clinics and Antenatal Beds
ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street Edinburgh, 8
3 30 P M Mr Eric Samuel Mechanical Syndromes following Partial Gastrectomy

Thursday, 20th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Prof J P Nuboer Recurrent Peptic Ulcer after Gastrectomy (Moynihan lecture)
UNIVERSITY OF LONDON
5 P M (Royal Veterinary College, Royal College Street, N W 1) Prof C W Emmens (Sydney) Effects of Anti œstrogens
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (Senate House, Malet Street, W C 1) Prof C H Waddington Significance of Developmental Biology
BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street W 1
8 P M Dr J W D Bull History of Neuroradiology (Presidential address)
MANCHESTER MEDICAL SOCIETY
8 P M (Staff House, University of Manchester) *Anæsthetics* Dr James Sneddon Presidential address
UNIVERSITY OF ST ANDREWS
5 P M (Physiology department, Queen's College, Dundee) Dr C C Booth Studies in Intestinal Absorption and Malabsorption

Friday, 21st

ROYAL SOCIETY OF MEDICINE
5 30 P M *Epidemiology and Preventive Medicine* Sir George Pickering, Sir Robert Platt Nature of Essential Hypertension
8 15 P M *Radiology* Dr E B D Neuhauser (Boston) Lesions Derived from Neuro enteric Canals
POSTGRADUATE MEDICAL SCHOOL
10 A M Dr B G B Lucas Physiological Aspects of Anæsthesia
4 P M Dr J F Goodwin Cardiomyopathy
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W C 1
3 30 P M Miss Edith Whetnall Deaf Child
MANCHESTER MEDICAL SOCIETY
9 P M (Medical School, University of Manchester) *General Practice* Dr Michael Balint Examination by the Patient
MEDICO CHIRURGICAL SOCIETY OF EDINBURGH
8 30 P M (Joint meeting with Royal Medico Chirurgical Society of Glasgow, 242, St Vincent Street, Glasgow, C 2) Dr W M Harrowes, Dr Gavin Arneil, Dr B E C Nordin, Mr James Ross That the Practice of Medicine is an Antisocial Activity

The Lancet · Saturday 22 October 1960

HYPERTENSION AND CEREBROVASCULAR DISEASE

JOHN MARSHALL
M.D Manc., F.R.C.P.E., M.R.C.P., D.P.M.
READER IN CLINICAL NEUROLOGY

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THE role of hypertension in the production of cerebro-scular disease is difficult to assess Pathologically, three pes of change are seen in the caroticovertebral vascular ee.

The carotid and vertebral arteries themselves, and their rger intracerebral branches, are affected by athero-sclerosis, which is characterised by accumulations of fat in the intima and various degrees of fibrosis The pathogenesis of atherosclerosis is still a matter of dispute and of much active research, but it has been suggested that hypertension may contribute in two ways

Paterson et al (1960) have demonstrated in 184 cases, a significant relation between the blood-pressure in life and the degree of atherosclerosis found at necropsy in the coronary and cerebral arteries They suggest that high blood-pressure ruptures the capillaries which frequently vascularise atheromatous plaques, and so increases the deposit of blood lipids in the vessel wall The other explanation is that high blood-pressure increases the rate of filtration of lipids from the lumen of the artery into the intima, for, though in laboratory animals raised blood-pressure does not seem to influence the development of spontaneous atherosclerosis, it does aggravate cholesterol-induced atherosclerosis (Bronte-Stewart and Heptinstall 1954)

The second type of pathological change—arteriosclerosis and arteriolosclerosis—is seen both in the carotid and vertebral arteries and in the smaller intracerebral arteries and arterioles Hypertrophy of the media and reduplication of the internal elastic lamina are characteristic, and it is generally agreed that this type of change is entirely due to hypertension (Hueper 1944)

The third type of change is replacement of the muscular and elastic elements of large arteries by fibrous tissue as age advances This may occur without notable changes in the intima or preceding hypertrophy of the media. It is often called senile arteriosclerosis, and although it is a normal manifestation of ageing, it may be aggravated by hypertension (Smirk 1957)

Hypertension may therefore be incriminated in greater or lesser degree in all three types of pathological change in the caroticovertebral arterial system

In assessing the exact role of hypertension in cerebrovascular disease a further difficulty arises, for the nature of essential hypertension is the subject of controversy

Platt (1947, 1959) considers that essential hypertension is a specific disease entity, thus some people have high and others normal blood-pressure according to whether they have the disease He "postulated (but did not claim to prove) that the disease might be due to a gene behaving as a mendelian dominant" An important part of the evidence in support of this type of inheritance was the observation that the blood-pressures of the siblings of a group of hypertensive subjects had a bimodal distribution, indicating that two populations were involved It was suggested that these populations comprised those who had, and those who had not, inherited the disease Further support for this view was provided by Morrison and Morris (1959), who observed that the systolic blood-pressures in a group of 302 London busmen, aged 45–60, whose parents had died between the ages of 40 and 64, likewise had a bimodal distribution The death of parents in middle age was assumed to be a crude indication of the presence of hypertension in the group

Pickering, on the other hand, considers that essential hypertension is not a specific disease entity, blood-pressure being distributed continuously throughout the population, as are height and intelligence. Those with so-called essential hypertension are merely an arbitrarily defined group taken from one part of the curve He postulated that the level of the blood-pressure is determined by both environmental and hereditary factors, the latter involving multiple genes rather than a single dominant gene (Hamilton, Pickering, Roberts, and Sowry 1954a, b, and c, Oldham, Pickering, Roberts, and Sowry 1960)

AGE OF PATIENTS

Age-group (yr)	Males	Females	Total
31–40		1	1
41–50	12	6	18
51–60	47	16	63
61–70	32	20	52
Total	91	43	134

The effective management of cerebrovascular disease must ultimately be based upon a proper understanding of the ætiological factors involved, hence it seemed important to try to ascertain the contribution of hypertension to cerebrovascular disease, and the nature of this hypertension

Method of Study

A series of 134 patients, aged 70 years and under, provided the basis of this study They had all previously had what was judged on clinical grounds to have been a non-embolic cerebral infarction.

These patients attended hospital for one day, during which they rested on a bed in the supine posture. Their blood-

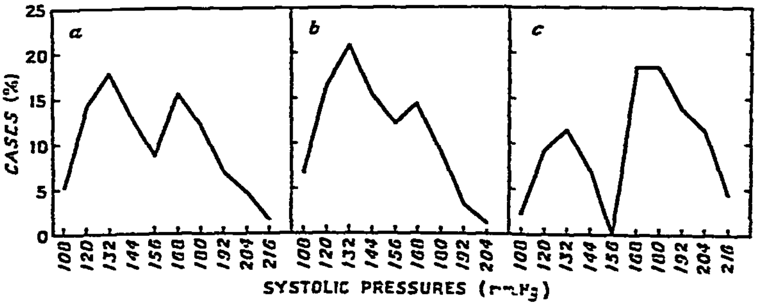


Fig 1—Distribution of systolic pressures (a) in 134 patients (b) in 91 males, (c) in 43 females.

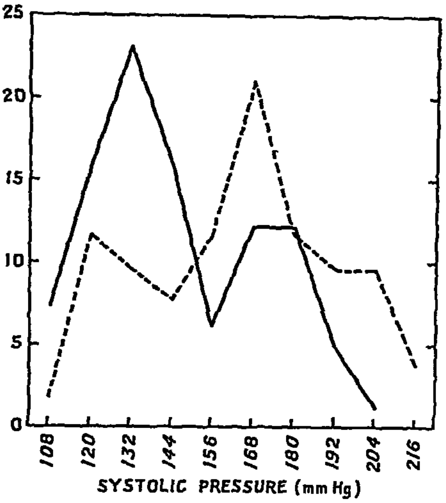


Fig. 2—Distribution of systolic pressures in 82 patients aged 60 and under (continuous line) and in 52 patients over 60 (interrupted line).

pressure was recorded hourly for six hours by specially trained nurses, who read the sphygmomanometer to the nearest even number. The first appearance of sounds was taken as the systolic pressure, and the change in the character of the sounds as the diastolic pressure. The figures from these six readings were averaged to give mean systolic and diastolic pressures, which are the blood-pressures referred to in this study.

During the one day in hospital the patients had a physical examination, chemical and microscopic examinations of the urine, estimation of the blood-urea and blood-cholesterol, an electrocardiogram, and a radiographic examination of the heart and skull. No patient with known secondary hypertension is included in the series.

On a later occasion the patients were interviewed, and a proforma was completed recording the age at death, and the cause of death, of their parents. In a few cases the proforma was sent to the patient by post, with instructions about its completion.

Results

The 134 patients included 91 men and 43 women. Their age distribution is shown in the table. When the systolic blood-pressures of the whole series are plotted on a graph, it can be seen at once that they have a bimodal distribution (fig. 1a), with modes at 132 and 168 mm Hg.

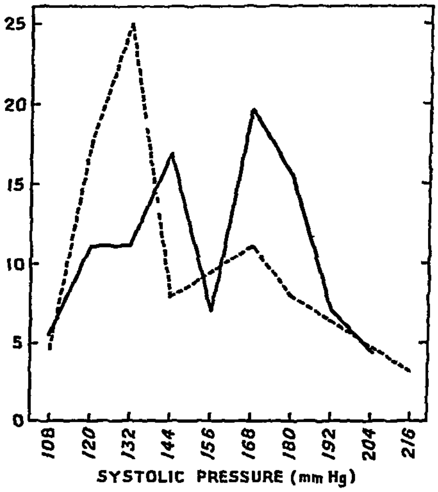


Fig. 3—Distribution of systolic pressure in 71 patients, one or both of whose parents died under the age of 65 (continuous line), and in 63 patients whose parents survived to 65 or over (interrupted line).

Examination of the sexes separately shows that the bimodality is less pronounced for men (fig. 1b), but more pronounced for women (fig. 1c).

As the series included patients up to 70 years of age, the bimodal distribution may possibly be due to the inclusion of older patients with high blood-pressure.

Evidence on this point is given in fig. 2, where the systolic pressures of the 82 patients aged 60 and under are plotted separately from those of the 52 patients over 60. This shows, in the older age-group, a definite shift to the right of the graph, with a mode of 168 mm Hg as against a mode of 132 for the younger group, though both groups still show a suggestion of bimodality. The mean of 152.0 mm Hg in the former differs significantly from that of 170.6 in the latter ($P < 0.001$).

Thus it seems that a factor affecting the level of blood-pressure emerges in some of the patients over 60, and that this factor may contribute to the bimodal distribution of the blood-pressures in the whole series.

That a group of patients with senile hypertension is not the full explanation of the bimodality in the whole series is shown in fig. 3, where the effect of dividing the patients into two groups, according to the age at death of their parents, is shown.

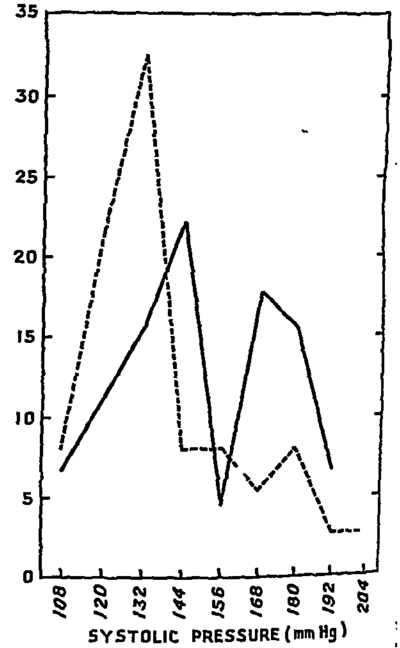


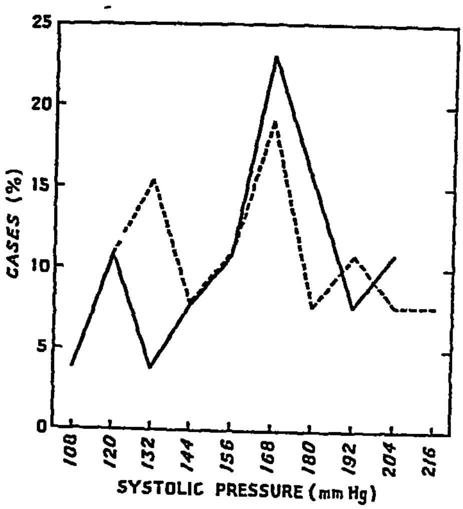
Fig. 4—Distribution of systolic pressures in 82 patients aged 60 and under: one or both of whose parents died under 65 (45 patients, continuous line), both of whose parents survived to 65 or over (37 patients, interrupted line).

The systolic pressures of patients, one or both of whose parents died under the age of 65, show a bimodal distribution with modes at 144 and 168 mm Hg. The systolic pressures of patients whose parents survived to 65 or over show little evidence of bimodality, but they have a prominent mode at 132 mm Hg.

Assuming more hypertension in the group of parents who died under 65 (Morrison and Morris 1959), hypertension in the parents seems to influence the production of hypertension in their children.

In order to remove the complication of senile hypertension, the systolic pressures of patients aged 60 and under were plotted in fig. 4. The pressures of patients, one or both of whose parents died under 65, clearly have a bimodal distribution, whereas the pressures of patients whose parents survived to 65 or over clearly have not.

The systolic pressures of patients over 60 years had a bimodal distribution irrespective of whether their parents died below or above the age of 65 (fig. 5). This indicates



5—Distribution of systolic pressure in 52 patients over 60 one r both of whose parents died under 65 (26 patients, continuous ine), and both of whose parents survived to 65 or over (26 patients, nterrupted line)

it the behaviour of their parents has ceased to matter, t the factor of senile hypertension is operative in some, t not all, the patients of this group

The systolic pressures have been presented first cause, being more easily recorded than the diastolic, y are generally believed to provide more reliable data the other hand, a rise in diastolic pressure is conered more sinister and more truly indicative of hypersion than a rise in systolic pressure The distribution the diastolic pressures in the whole series is shown, fig 6, to have a bimodal distribution with modes at and 104 mm Hg This bimodality is again more minent in the women than the men

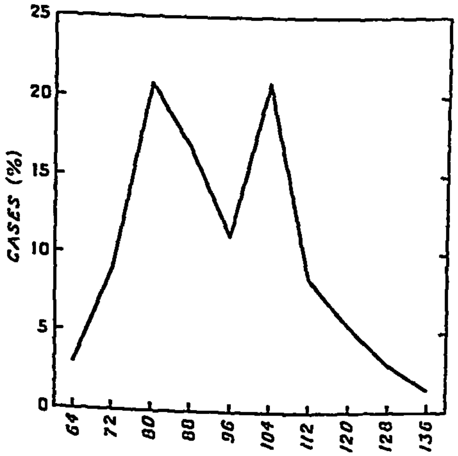


Fig 6—Distribution of diastolic pressure in 134 patients

omparison of the over-60 group with the 60-andler group again shows a shift to the right with age, h a markedly bimodal distribution in the older ageup (fig 7) This bimodality persists irrespective of age of death of their parents (fig 8), confirming the lings with regard to systolic pressures

xamination of the influence of the age of death of the ents in the patients aged 60 and under, who were sumably less affected by senile hypertension, we again l a suggestion of bimodality in those whose parents died under 65 (fig 9), but no such suggestion in those whose parents died at 65 or over

Discussion

In these patients with cerebrovascular disease the blood-pressure had a bimodal distribution This was partly due to a group with raised blood-pressure among the patients over 60 The rise in blood-pressure was unrelated to the age at death of the parents The blood-pressures of patients aged 60 and under also had a bimodal distribution, but this bimodality was only present in patients one or both of whose parents died under the age of 65

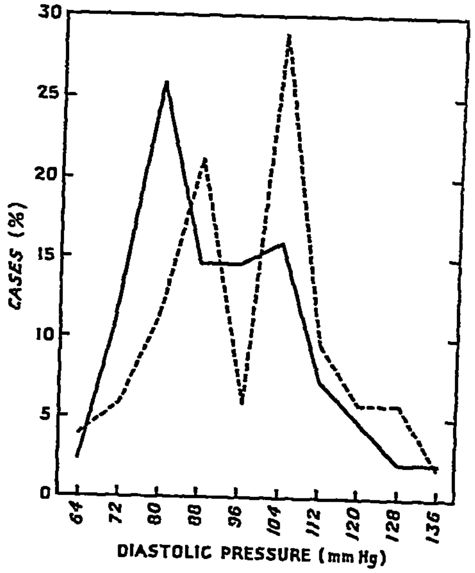


Fig 7—Distribution of diastolic pressures in 82 patients aged 60 and under (continuous line), and in 52 patients over 60 (interrupted line)

The first objection which must be met is that the bimodal distribution of blood-pressures might be due to digit preference (Oldham et al 1960) The tendency to

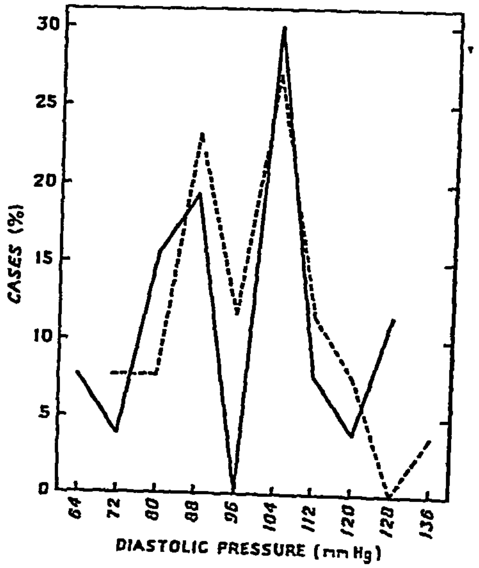


Fig 8—Distribution of diastolic pressures in 52 patients over 60 one or both of whose parents died under 65 (26 patients continuous line), and both of whose parents survived to 65 or over (26 patients, interrupted line)

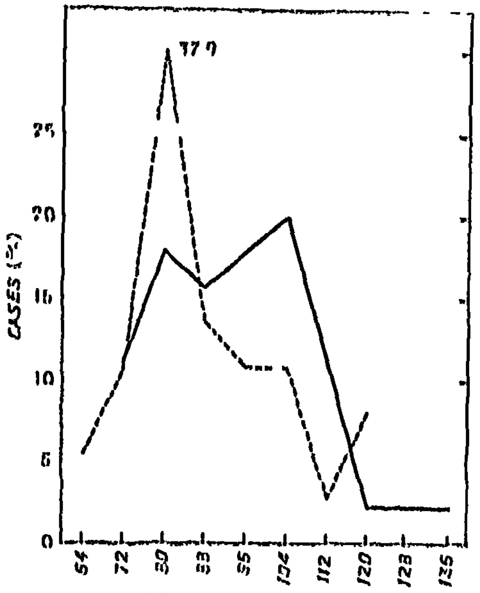


Fig. 9.—Distribution of diastolic pressures in 62 patients aged 60 and under: one or both of whose parents died under 65 (15 patients, continuous line); and both of whose parents survived to 65 years or over (47 patients, interrupted line).

take blood-pressure readings to the nearest 5 or 10 mm. mark, the desire of the clinician to classify the patient as hypertensive or non-hypertensive, or the instructions of insurance companies about the action to be taken if the blood-pressure exceeds a certain level, may all induce a degree of conscious or subconscious digit preference. These objections cannot be applied to the present study. The blood-pressures were read to the nearest even number, and the observers had no instructions or incentive other than to record the blood-pressure as accurately as possible. Moreover, the blood-pressure figures used in this study were the mean of six readings taken under constant conditions. Digit preference cannot therefore account for the bimodal distribution curves.

A second objection is that the emergence of an apparently bimodal distribution is solely a matter of chance. The constancy with which bimodality has been demonstrated in the various samplings of this study, and in other studies (Platt 1959, Morrison and Morris 1959), indicates that this objection is without substance.

The results of this study indicate that the blood-pressures of a series of patients with cerebrovascular disease are not distributed continuously as in a normal distribution curve, but that they follow a bimodal curve. This bimodality springs partly from the group, among patients over 60, in whom the blood-pressure had risen more than in their fellows. The data of this group did not suggest that their hypertension could be related to the age at death of their parents. In the patients whose parents both survived to 65 or over, as in those of whom one or both parents died under 65, the systolic and diastolic pressures both showed a bimodal distribution. There is, therefore, no evidence to support the existence of a hereditary factor in this group. Indeed, these data offer no hint as to why some patients over 60 develop hypertension and others do not. It is useful, however, to separate those with hypertension as a group from the other patients with cerebrovascular disease, and to refer to them by a non-committal term—e.g., as patients with senile hypertension—thus distinguishing them from patients under 60 with hypertension.

The situation for patients of 60 and under with cerebrovascular disease is different. They likewise showed a bimodal distribution of blood-pressures, but this was entirely due to the contribution made by those patients of whom one or both parents died under the age of 65. In the patients whose parents survived to 65 or over, the blood-pressures—both systolic and diastolic—showed a distinctly unimodal distribution. Here, therefore, it seems likely that the appearance of a group with raised blood-pressure is caused by a hereditary factor—probably, as Platt (1947, 1959) has suggested, due to a mendelian dominant. This group contrasts clearly with the group of hypertensive patients over 60, and emphasises the importance, in studies of the role of hypertension in cerebrovascular disease, of not treating as a uniform group all patients with hypertension.

It would be valuable to correlate the pathological changes which have been described in cerebrovascular disease with the groupings delineated by this study. Thus the patients with senile hypertension might be expected to show changes of senile arteriosclerosis. Those with hereditary hypertension might have arteriosclerosis and arteriolosclerosis of the type characterised by hypertrophy of the media with reduplication of the internal elastic lamina.

The influence of hypertension, either senile or the hereditary type, on the lesions of atherosclerosis is hard to predict in view of the many other factors involved in the development of atherosclerosis, though, as already indicated, hypertension is probably an aggravating influence (Paterson et al. 1960). These pathological correlations are at present tentative, but they could be placed on a firm basis by carefully following a group of patients of the type described here.

This study also casts some light on the current controversy as to the nature of essential hypertension. The repeated finding of bimodality in the distribution of the blood-pressure of various groups of subjects cannot be dismissed as due to observer-error or chance. Bimodality has now been demonstrated in the blood-pressure distribution of the relatives of hypertensive patients, a group of normal busmen, and a group of patients with cerebrovascular disease. The conclusion seems inescapable that the level of blood-pressure cannot be regarded as a feature distributed continuously throughout the population, but that there are different groups, the recognition and study of which will aid our understanding of hypertension and of its relation to cerebrovascular disease.

Our approach to cerebrovascular disease must not be limited solely by considerations of morbid anatomy—trying to distinguish both in life and after death between embolic infarction, non-embolic infarction, and hæmorrhage. It must also take into account dynamic factors in the life-histories of patients, which may provide fruitful clues to ætiology, and lead to better means of managing cerebrovascular disease than our present inadequate methods.

Summary

In 131 patients with a history of cerebral infarction, the blood-pressures showed a bimodal distribution. This was due, among patients over 60, to a group with hypertension which was unrelated to the age at death of their parents.

The blood-pressures of the patients aged 60 and under also had a bimodal distribution, but this was confined

to patients whose parents (one or both) died under the age of 65

The significance of these findings is discussed in relation to the ætiology of hypertension and pathological changes in blood-vessels

I wish to thank the Nuffield Foundation for their generous support of our studies in cerebrovascular disease, of which this forms a part

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ENVIRONMENTAL INFLUENCES AND ARTERIAL BLOOD-PRESSURE

RICARDO CRUZ-COKE
M D
PHYSICIAN AND INSTRUCTOR IN MEDICINE TO THE HOSPITAL AGUIRRE, UNIVERSITY OF CHILE SCHOOL OF MEDICINE

IN analysing the nature of the inheritance of hypertension it has been suggested that environmental factors are more important than genetic factors in determining the degree of deviation from the norm in the population at large Furthermore it has been supposed that environmental factors are largely responsible for the rate and pattern of the rise of blood-pressure with age (Pickering 1955, Oldham et al 1960) Clearly arterial pressure, like height or weight, is a constitutional human phenotype which is determined by the growth of a genotype through successive environments Thus, in general conformity with biological theory, the phenotype variation can be studied by means of frequency-distribution curves in a general-population sample To know the extent of the environmental influences in arterial pressure one must study the shape and variation of the tension curves I have examined the evidence for environmental influences on arterial pressure accordingly

Variation of Tension Curves

When the diastolic arterial pressure of a general-population sample is grouped in units of 10 mm Hg and plotted against frequency, a mathematically definable bell-shaped curve is obtained

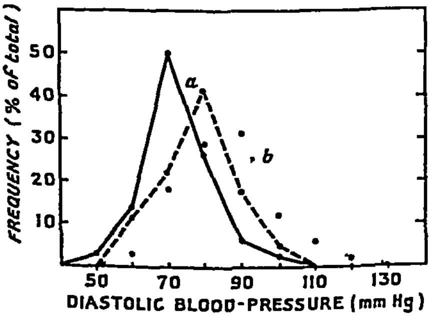

Fig 1—Frequency-distribution curves of diastolic blood-pressure with age

(*a*) 51 apparently healthy males of the National Health Service of Employees, Chile, followed for 15 years, continuous line shows first readings when aged 20–29 years, and interrupted line shows last readings when aged 35–44 years (*b*) Dotted line shows 75 readings of apparently healthy males aged 50–59 years in the same Service. (Data from Cruz-Coke [1959])

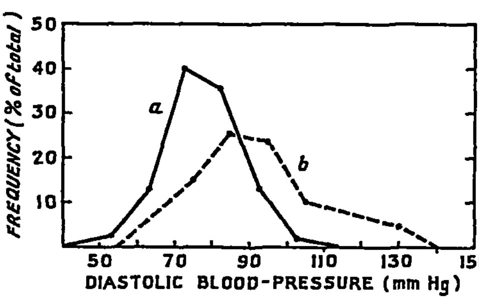

Fig 2—Frequency-distribution curves of diastolic blood-pressure with age

(*a*) Continuous line represents values for 180 English males aged 30–39 years read in London (data from Pickering [1955]), and (*b*) interrupted line represents 895 English males aged 20–38 years read in Tripolitania (data from Graham [1945])

In fig 1 I have constructed in a continuous line a tension curve, skewed and with a positive kurtosis or degree of " peakedness " (Arkin and Colton 1939) The shape of this curve shows a significant variation if the same population sample is measured 15 years later, the later (interrupted) curve shows a low positive kurtosis and a shift in the mean from 72 8 to 79 mm Hg In the same figure the dotted line represents the curve for an older group of the same population sample—flatter and shifted to the right, with a mean of 85 7 mm Hg These observations seem to show that the influence of age determines the variation in shape of a tension curve, and the rise in the mean (Moore 1958) The fact that the curve cannot reach high values without change of the kurtosis suggests that transformation of the kurtosis is the essential key in the variation

One can conclude, therefore, that the increase of arterial pressure in a general-population sample is a function of the variation in degree of the kurtosis, and that the rise of pressure with age is secondary in the changing process of the shape of a tension curve

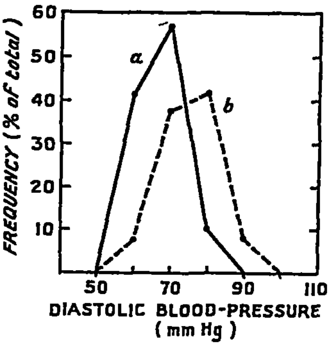

Fig 3—Frequency-distribution curves of diastolic blood-pressure of 50 males with a mean age of 21 years born in Cuzco

(*a*) Continuous line represents 29 males who stayed in Cuzco, and (*b*) interrupted line represents 21 males who emigrated to Lima (Data from Cruz-Coke [1960])

Influence of Environment

The possibility that environmental factors are responsible for the variation in the tension curve, and consequently for the rate of rise of blood-pressure with age, was suggested by Pickering in 1955 Nevertheless the flattening of a tension curve under the direct influence of environment has not yet been demonstrated Theoretically this influence can be analysed by combining data from Pickering (1955) and Graham (1945)

In fig 2 I have plotted as a continuous line the tension curve of English males aged 30–39 years, and as an interrupted line that of other English population samples of the same age and sex This second curve has the characteristic shape of an " old " English population sample (see fig 4) How can a " young " curve be flattened like an " old " curve without the influence of age? Graham's findings explain this fact The blood-pressure of Graham's group was read in a training area in Tripolitania after 2 years in desert warfare in an armoured brigade This group had changed their peaceful "ecologic niche" (Odum 1959) in England for a stress environment associated with

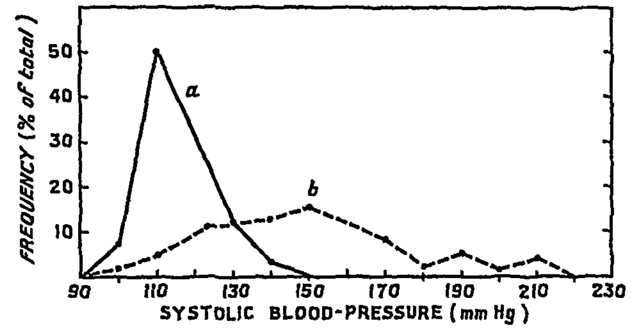

Fig 4—Frequency-distribution curves of systolic blood-pressure with age

(*a*) Continuous line represents 896 Indian males from Macusani, *with a mean age of 62 5 years (data from Ponce Barreda [1959]), and* (*b*) interrupted line represents 98 English males aged 60–69 years (data from Pickering [1955])

anxiety and strong affective states of mind Thus, roughly, the ecologic factors probably operating through the mind were responsible for the change from a "young" curve to a flattened and aged one, and the rise in mean blood-pressure from 75 8 to 90 mm Hg was a function of the decrease of the positive kurtosis

In view of the suggestion of Neel (1958), I obtained direct evidence in Peru of environmental influence on arterial pressure (Cruz-Coke 1960) by analysing two subsamples of a homogeneous population, one being in rapid cultural transition from a primitive society to the stress of "Western" civilisation

From the archives of the Central Police Hospital in Lima 50 policemen, born in Cuzco in the eastern Andean highland, were chosen by chance 29 of them had stayed in their ecologic niche in a primitive society living in the past until coming to Lima to enter the police school The other 21 had emigrated to Western civilisation in Lima some years before entering the police school, and had therefore worked in a new ecologic niche The two subsamples were comparable by age and anthropological data A significant difference appeared on analysing their tension curves when they *first* entered the police school In fig 3 the "Western" curve is flattened and shifted to the right in comparison with the "eastern" curve which has a high positive kurtosis

This direct evidence shows that this change of environment was responsible for the transformation of the kurtosis and for the rise of mean pressure from 65 1 to 76 8 mm Hg But the evidence needs confirmation in an opposite direction—namely, by showing that an "old" population curve with a high positive kurtosis is not *influenced by a modern environment*

Indirect evidence of this possibility can be obtained if the tension phenotype of an old human population of a Caucasian subspecies is compared with an American human subspecies of the same age In fig 4 the tension phenotypes of a population sample from Macusani, Peru (Ponce Barreda 1959) are compared with another sample of the same age and sex from London Despite their age the native Andean population has a "young" systolic tension curve *with a mean of 115 mm* Hg against a mean of 153 for the English population sample This strong difference arises because the Macusani population, which is absolutely *isolated from the modern* world and living in the past, has an ecologic niche which has not changed from the times of the empire of the Incas

Discussion

The evidence here analysed shows clearly that the increase of arterial pressure with age is produced mainly by environmental factors operating in the population at large Without doubt the increase in the mean tension curve is caused essentially by the variation in the kurtosis Theoretically, irrespective of age, a genotype which has *not been influenced by environment* shows a phenotype curve with a high positive kurtosis (fig 4, continuous line), and after stronger environmental influences the curve is flattened and shifted to the right, *with a higher mean (fig* 4, interrupted line) The rate of change of the kurtosis is determined by the intensity of the environmental influence, a high rate of variation is shown in the flattened curve of fig 2 (Graham 1945), and a very slow rate in the Macusani skewed curve of fig 4 The high blood-pressure appears to be directly related to the intensity of the environmental influences and is irrespective of age In Graham's curve, 27% of a young population sample crossed the official American lower limit of diastolic "hypertension" (*American Medical Association Committee* 1960) In the Macusani curve, however, any male could cross the systolic hypertensive limit of 150 mm Hg

Besides considering environmental factors one must not forget the genetic component in the determination of arterial pressure The phenotype for tension of a population is the end result of the interaction of certain environmental variables and a genetic predisposition, probably determined by multiple genes (Neel 1958) Thus the variation in the tension curve is determined by this interaction, in which the environmental factors play the largest part

Conclusion

The variation of the frequency-distribution curves of arterial pressure in a population sample is directly influenced by the intensity and duration of environmental factors and is irrespective of age

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PREVENTION OF URINARY INFECTION AFTER PROSTATECTOMY

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WE have previously described a closed apparatus for the aseptic drainage and irrigation of the bladder, and a method of disinfecting non-boilable cystoscopes and resectoscopes with a mixture of chlorhexidine ('Hibitane') and mercuric oxycyanide (Miller et al 1958) After the introduction of these methods in the Bristol Royal Infirmary, the incidence of urinary infection after transurethral and retropubic prostatectomy fell from 74% to 23%

As previously reported, some of the infections which still occurred were probably caused by bacteria which had entered the urethra before operation We therefore decided to disinfect the urethra We describe here the effect of this measure, and report the results of applying all the precautions in another hospital

Materials and Methods

Only patients whose urine was initially sterile were included in the investigation None were given prophylactic antibiotics or chemotherapy The bacteriological methods were those previously described

As a combined urethral disinfectant and lubricant, we used a solution of chlorhexidine (0 05%) in glycerol (as recommended by the manufacturers, Imperial Chemical Industries) As soon as the patient was anæsthetised, 5 ml. was instilled into the urethra and retained by means of a penile clamp, which was released after the patient was put on the operating-table, 5 to 10 minutes later

Results

In March, 1958, urethral disinfection was added to the other precautions previously introduced in the Bristol Royal Infirmary Thereafter the incidence of urinary infection fell again, from 23% to 5% The results from the beginning of the investigation are summarised in table I

Infection could usually be prevented when the several measures were used in combination, but the value of closed drainage alone was still doubtful The doubt was resolved by repeating the investigation in Southmead General Hospital, where the routine methods were similar to those formerly used in the Infirmary From December, 1958, the new methods were introduced in a different order from that previously adopted, beginning with the theatre precautions—namely, urethral disinfection and the improved disinfection of cystoscopes (The cystoscopes were disinfected in an aqueous solution of chlorhexidine 1/5000, without the admixture of mercuric oxycyanide) There was a fall in the incidence of those infections which started within 18 hours of operation, but the overall incidence was not greatly reduced until April, 1959, when closed drainage and irrigation were brought into use The incidence of infection in patients treated with full precautions then fell to 7%, from its former level of 97% (table II) This gratifying result was similar to that previously obtained in the Infirmary, and confirmed our belief in the need to combine the precautions

TABLE I—INCIDENCE OF URINARY INFECTION AFTER TRANSURETHRAL AND RETROPUBIC PROSTATECTOMY IN THE BRISTOL ROYAL INFIRMARY

Extra precautions	Patients with sterile urine before operation	Number with infection after operation
None (April, 1955–November, 1956)	57	42 (74%)
Closed drainage and irrigation (November, 1955–October, 1957)	44	25 (57%)
The same + improved disinfection of cystoscopes (November, 1957–March, 1958)	30	7 (23%)
The same—disinfection of urethra (March, 1958–December, 1959)	75	4 (5%)

There were only 8 infections (6%) among the 136 patients who were treated with full precautions in the two hospitals 12 other patients started with full precautions, but closed drainage had to be discontinued when brisk bleeding immediately after operation caused their catheters to become so firmly blocked by clot that neither the closed irrigation apparatus nor an ordinary bladder syringe was sufficient to clear them The catheters had to be removed and replaced, after which 8 of the 12 patients became infected Their inclusion in the series brings the incidence of infection in the two hospitals together to 16/148 (11%), compared with 71/87 (82%) before any of the special precautions were introduced.

TABLE II—INCIDENCE OF URINARY INFECTION AFTER TRANSURETHRAL AND RETROPUBIC PROSTATECTOMY IN SOUTHMEAD GENERAL HOSPITAL

Extra precautions	Patients with sterile urine before operation	Number with infection after operation
None (May, 1958–November, 1958)	30	29 (97%)
Disinfection of urethra—improved disinfection of urethral instruments (December, 1958–March 1959)	21	13 (62%)
The same—closed drainage and irrigation (March, 1959–December, 1959)	61	4 (7%)

Discussion

Urinary infections after prostatectomy are mostly caused by organisms derived from other patients by cross-infection (Ørskov 1952, 1954, Gillespie 1956, Dutton and Ralston 1957) Sometimes, however, the organisms come from the patient's own body (Miller et al 1958, Linton 1960) But whatever their source, bacteria can rarely cause urinary infection unless they are allowed to pass up the urethra or the indwelling catheter Hence every effort should be made to destroy bacteria in the urethra before operation, and to exclude them during and after operation The application of these principles in our two hospitals reduced the incidence of infection from 83% to 11% Moreover, about half of the infections which made up the residual 11% were caused by the removal and reinsertion of catheters on the few occasions when brisk postoperative bleeding led to intractable obstruction by clot It is evidently important to watch patients closely during the first hour or so after operation, and to irrigate the bladder promptly in the event of brisk hæmorrhage, simply in order to avoid having to dismantle the closed drainage system If despite this, the catheter has to be replaced, or the apparatus disconnected so that a bladder syringe or evacuator can be used, then the procedure should preferably be performed in the theatre, with full aseptic precautions

The efficient disinfection of non-boilable resectoscopes and cystoscopes has always been difficult Cleansing with soap and a small brush, followed by thorough rinsing with running water and immersion in a vertical position for 15 minutes in an aqueous solution of chlorhexidine 1/5000 has been found satisfactory The addition of mercuric oxycyanide to a concentration of 1/2000 increased the margin of safety (Miller et al 1958, Linton 1958) Disinfection may be more rapidly achieved by immersion for 2 minutes in a solution of chlorhexidine (0 5%) in 70% alcohol This method has proved to be satisfactory in another Bristol hospital, where it was used for 2 years without damaging the instruments

Disinfection by heat, if practicable, is preferable to chemical methods The "pasteurisation" technique recently described by Francis (1959) may in future prove to be the method of choice for non-boilable urethral instruments, but we have not yet employed it

The benefits of avoiding postoperative infection will be reduced unless the urine is kept sterile when preoperative drainage is necessary This can usually be achieved by employing closed aseptic drainage when acute retention of urine is treated by an indwelling catheter (Miller et al. 1960) The narrow-bore ' Portex ' catheter described by Gibbon (1958) is specially suitable for such cases.

In our experience, it is the organisms which have recently appeared in the urine which are particularly likely to invade the blood-stream (Gillespie et al 1960) Every effort should therefore be made to prevent added infection at operation or afterwards All patients should be treated alike, whether previously infected or not

The routine use of these special preventive measures has made postoperative urological infection comparatively rare though previously it was almost inevitable, and has greatly reduced the " load of infection " of antibiotic-resistant gram-negative bacilli in the two hospitals It has even been possible to give up routine bilateral vasectomy at the end of prostate operations

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CONFUSION IN THE ELDERLY

SOME COMMON REMEDIABLE CAUSES

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CONFUSIONAL states in the elderly arise with comparatively minor upsets which would hardly produce malaise in younger people. No doubt the basic reason for the severer effect in old people is their very small margin of reserve, also they often have other conditions, such as arteriosclerosis, anæmia, diminished renal function, and borderline malnutrition and dehydration (Berk 1958) But the conclusion that the condition is a " senile dementia " may lead to much avoidable suffering, not only for the patient but also for the relatives

Once old people have to stay in bed, the rapid development of loaded bowel and bladder, incontinence, dehydration, bedsores, and terminal bronchopneumonia or urinary infection must be anticipated Perhaps the most important single factor in the care of the elderly sick is to keep them out of bed in a comfortable chair for at least a few hours every day

Loaded Bowels

This condition is commonly found when elderly patients are admitted solely because of mental confusion Relief of the constipation restores their mental equilibrium In some cases a fæcal mass collects, and acts as a ball valve, allowing fluid fæces to pass from above Mechanical bladder obstruction may also be caused, and incontinence then adds to the patient's distress Palpation of the abdomen often does not reveal the true state of affairs, and the history can be misleading because the bowel action may appear to be regular Digital examination of the rectum will usually, though not always, make the situation clear, and it is then simple enough—with enemas, olive oil, suppositories, and gentle laxatives such as bisacodyl (' Dulcolax ')—to relieve the constipation Bisacodyl is a useful laxative in such cases because it acts by contact with the large bowel and is therefore unlikely to precipitate an acute intestinal obstruction or ruptured appendix After relief of the constipation the mental confusion may take a week or two to clear

Examples

A woman, aged 79, was admitted to hospital with confusion, restlessness, and diarrhœa She was mildly dehydrated, and rectal examination revealed a loaded bowel with overflow incontinence She was treated with fluids, salt, and enemas, and she was discharged rational and relieved

A man, aged 83, admitted to hospital with mental confusion, was found to have intestinal obstruction due to impacted fæces which were not felt on abdominal or rectal examination He also had right-lower-lobe pneumonia (confirmed by X-ray), arteriosclerosis, congestive cardiac failure with an enlarged heart, and chronic bronchitis and emphysema The hæmoglobin was 70%, and the blood-urea 74 mg per 100 ml. He was treated with antibiotics, oxygen, digoxin, daily enemas and flatus tube, liver and iron, and carbachol by mouth He passed an enormous stool on the 2nd day, and made a rapid recovery. He was discharged rational after 2 weeks He had refused a barium-enema, but at outpatient follow-up a month later he was well and mentally normal

Anæmia

Even a slight degree of anæmia can by itself cause severe mental confusion, often maniacal in character An increase in the hypoxic state of the cerebral cortex, which is already arteriosclerotic, tips the balance of sanity Restoration of the hæmoglobin level is not always simple, but provided the anæmia has not been present too long, the mental state can be restored to normal Examination of the blood may suggest an iron-deficiency anæmia, but the exhibition of iron alone, by any route, may not improve the situation Malabsorption and vitamin deficiency play a major part in causing these anæmias, and the whole gamut of therapy may be required—including ascorbic acid, vitamin B_{12}, folic acid, thyroid extract, androgens, œstrogens as appropriate, and even small initial blood-transfusions In a simple iron-deficiency anæmia improvement with oral or intramuscular iron can be expected within 2 weeks Even in megaloblastic anæmia iron is still required in the elderly, as well as the appropriate " factor ".

Examples

A woman, aged 68, was admitted to hospital in a confused state on a 3-day order Her hæmoglobin level was 65% After treatment with iron and vitamins she was discharged rational 3 months later she was readmitted again confused, and with anæmia and malnutrition She was treated as before and, after 3 months, again discharged in a stable mental state to a welfare home

A woman of 76, admitted to hospital confused and noisy, had a hæmoglobin level of 55% She was treated with intramuscular iron and vitamins, but, after 10 days, the hæmoglobin was 45%. She was then given folic acid, vitamin B_{12}, and thyroid extract (starting with gr $^1/_8$ daily, slowly increased to gr $^1/_2$ daily) The hæmoglobin was 50% after two weeks, and 65% after a further 4 weeks She became rational and cooperative when the hæmoglobin began to rise, and she has remained so ever since

The following case illustrates how the relief of two conditions may not be sufficient to restore mental balance, although further improvement of the physical state may do so

A woman of 82 was admitted to hospital confused and rulous She was dehydrated, she had auricular fibrillation d a hæmoglobin level of 60%, and hard fæces were palpable tally The constipation was relieved, she was rehydrated, d tranquillisers were given but she was still confused She s then treated with iron and vitamin B_{12} 2 weeks later her ndition had improved and she was rational

Dehydration

Dehydration, which occurs readily in old people, can be e sole cause of confusion Renal function in the elderly below par, and a fixed urinary specific gravity of around 10 is common (Hazell 1957) Thus, to excrete urea and her waste products, more water and salt must be lost nless intake is adequate, salt, as well as water, depletion llows, and the patient does not then feel thirsty ehydration develops, and eventually uræmia supervenes ich a patient, given salt by mouth, can regain the desire drink within less than an hour, and this can be life-ving, provided that copious fluids are then given lalnutrition and vitamin deficiency—including frank urvy—may be associated with dehydration (Berk 1958) ld people all too often today live on a diet of bread-and-utter, cake, and tea, when they become ill there may be o-one to give them even fluids

xamples

A man of 83 was admitted to hospital confused and dehy-rated with a hæmoglobin of 60% He was treated by rehydra-on, and with iron and vitamins, and he was discharged after month quite well in himself At outpatient follow-up 2 months ter his hæmoglobin was 70%

A man of 71 was admitted to hospital confused, with broncho-neumonia, dehydration, malnutrition, double incontinence, nd scurvy His hæmoglobin level was 70%, the Hess test was ositive, the blood-urea 70 mg per 100 ml, plasma-proteins 5 mg per 100 ml (albumin 4 9 and globulin 2 6), serum-scorbic-acid 0 25 mg per 100 ml, and serum-vitamin-B_{12} evel 275 µµg per ml He was treated with antibiotics, tran-uillisers, enemas and olive oil, massive doses of vitamins 'Parentrovite' intramuscularly and ascorbic acid 450 mg by outh daily), and iron by mouth He became sensible after 3 eeks

Bronchopneumonia

Bronchopneumonia may cause delirium in patients of ll ages, but I mention it particularly because of the nsidious way it can arise in the elderly There may be no ever or dyspnœa to attract attention to the lungs, the only ign being the onset of confusion Sometimes the only lue to the presence of bronchopneumonia may be apathy and listlessness, and a tendency to sink down in bed. Examination of the lungs—and particularly the bases posteriorly—will reveal typical fine crepitations The response to antibiotics is often dramatic

Examples

A man of 86 was admitted to hospital with mental confusion, having had a cough for 4 days after an attack of "flu" Paraldehyde was necessary to control him Bronchopneumonia with dehydration was diagnosed. He was treated with penicil-lin, and discharged rational 4 months later

A man of 81, admitted to hospital with mental confusion, was unable to give a history He had a left hemiparesis (old stroke), and bronchopneumonia, and he was treated with antibiotics, tranquillisers, and physiotherapy He was discharged after 2 months, recovered

Other Disorders

Any serious disorder in the elderly can present as temporary mental confusion

A man of 79, admitted to hospital confused and disorientated, had a history of precordial pain for 12 days, and an electro-cardiogram showed an anterior infarct He was treated with morphine, digoxin, and tranquillisers, and he was discharged mentally normal after a month 9 months later, at outpatients, his mental state was still normal

A woman of 84, with diabetes mellitus which was controlled by chlorpropamide 200 mg daily, developed gangrene of the foot Her hæmoglobin was 35%, and she was generally confused, eating her own fæces A whole blood transfusion of 1 pint was given, and a week later the hæmoglobin was 55% There was a sharp line of demarcation at mid-foot level, and she was still confused, with coprophagia Above-knee amputation was performed, and she made an uneventful recovery, getting up after 2 days 2 weeks after operation she became mentally rational and well behaved, and the stump was well healed at 3 weeks

Other ætiological factors of confusion enumerated by Flint and Richards (1956) in 207 out of 242 elderly people, include cerebral disease (82), heart-failure (53), pulmonary disease (46), and uræmia (26) The remainder were anæmia, hepatic failure, avitaminosis, endocrine disorders, drugs, cancer, injuries, and miscellaneous infections The cause of confusion in half their cases was extracerebral.

Conclusions

The object of this paper is to draw attention to some common reasons for reversible mental confusion in elderly patients admitted to a geriatric unit in the Midlands Blocked bowels, anæmia, dehydration, and malnutrition can be treated in the home with the help of the district nurse and the various public health and welfare services, especiallv the home help service and "meals on wheels"

Emphasis is laid on the value of rectal examination in the elderly, and on the insidious onset of anæmia, dehydration, and bronchopneumonia

I should like to acknowledge Dr Kenneth Hazell's help and encouragement in the preparation of this paper, and the assistance of colleagues and staff at New Cross Hospital, Wolverhampton

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HÆMOGLOBINURIA AMONG ADULT NIGERIANS DUE TO GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY WITH DRUG SENSITIVITY

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The presence of the glucose-6-phosphate dehydrogenase deficiency trait in Nigeria was described in a previous communication (Gilles et al 1960) It was then suggested that some of the cases of hæmoglobinuria occurring in adult Nigerians, often summarily dismissed as "blackwater fever", were more likely to be drug-induced hæmolytic anæmias in patients who were carriers of the trait We believe this to be true of the patients we describe here

Case-reports

Case 1 —Male Nigerian (Yoruba), aged 27, with 5 days' history of abdominal pain with diarrhœa, joint pains, and fever He had sulphonamide drugs for his diarrhœa 2 days before the onset of "black urine" which had persisted for 3 days before admission He admitted having taken a mixture of naphthalene mothballs and sugar 2 days before the onset of hæmoglobinuria He looked pale and ill, his blood-pressure was 140/90 mm Hg The liver was palpable 2 fingerbreadths below the costal margin The spleen was not palpable His temperature was 101°F He received a transfusion of 2 pints of blood and was given chloroquine and cortisone Hæmolysis stopped 24 hours after admission

Investigations —Blood-urea 107 mg per 100 ml , group A rhesus +ve, hæmoglobin 4 6 g per 100 ml , mean corpuscular hæmoglobin concentration 27%, hæmatocrit value 15%, alkali-resistant hæmoglobin, less than 1% The direct Coombs test was negative in all dilutions, and there were no cold agglutinins Methæmoglobin was absent from the plasma The red-cell fragility was normal A few *Plasmodium falciparum* rings were found in a thick blood-film

Oxyhæmoglobin was found on spectroscopic examination of the urine The bone-marrow was normal The Kahn test was negative

The glucose-6-phosphate dehydrogenase rapid-screening test demonstrated low enzymatic activity (Motulsky 1959)

Case 2 —Male Nigerian (Yoruba), aged 29, with 3 days' history of fever, headache, and joint pains He attended the university dispensary and was given tablets of aspirin, phenacetin, and caffeine, one tablet three times daily (Total phenacetin taken 0 9 g) After 48 hours he developed hæmoglobinuria and was referred to hospital for admission He looked ill and was jaundiced but not pyrexial There was no enlargement of the liver or spleen His blood-pressure was 145/90 mm Hg He was treated with cortisone

Investigations —Blood-urea 56 mg per 100 ml , hæmoglobin genotype AS, hæmoglobin 6 6 g per 100 ml , mean corpuscular hæmoglobin concentration 38%, hæmatocrit value 20% The direct Coombs test was negative in all dilutions, and there were no cold agglutinins Methæmoglobin was found on spectrophotometric examination of the plasma Malarial parasites were absent from a thick blood-film

Oxyhæmoglobin was present in the urine

The glucose-6-phosphate dehydrogenase rapid-screening test demonstrated low enzymatic activity

Case 3 —Male Nigerian (Yoruba), aged 25, with 4 days' history of pain in the left side of the chest and 2 days' history of drowsiness followed by pain in the left hypochondrium, backache, and the passage of " black urine " For the past 3 days he had been taking tablets of aspirin, phenacetin, and caffeine, one tablet three times daily and on the day before admission an unidentified powder (Total phenacetin taken 1 5 g) The patient looked ill, his temperature was 102°F, his blood-pressure 100/70 mm Hg He was jaundiced, pale, and the spleen, palpable 3–4 fingerbreadths below the costal margin, was tender The liver was not palpable He was treated with chloroquine Hæmolysis stopped on 3rd day after admission

Investigations —Blood-urea 62 0 mg per 100 ml , group B rhesus +ve, hæmoglobin genotype AA, hæmoglobin 8 9 g per 100 ml , hæmatocrit value 26%, alkali-resistant hæmoglobin less than 1% The direct Coombs test was negative in all dilutions, and there were no cold agglutinins Methæmoglobin was absent from the plasma There were no malarial parasites in a thick blood-film

Both methæmoglobin and oxyhæmoglobin pigments were found in the urine The bone-marrow was normal The Kahn test was negative

The glucose-6-phosphate dehydrogenase rapid-screening test demonstrated low enzymatic activity

Discussion

It is generally agreed that " blackwater fever " does not develop in the adult indigenous inhabitants of a holoendemic malarious area so long as they are left undisturbed in their endemic environment If transmission of malaria is reduced by measures such as incomplete entomological control or injudicious use of antimalarial drugs, blackwater fever may appear in the community (Maegraith 1952) It is believed that this is largely due to the creation of a sensitive state resulting from partial loss of hard-earned immunity which leads to sharp hæmolysis upon successful reinfection with *P falciparum* (Adams and Maegraith 1960) All the three patients investigated lived in and around Ibadan (a holoendemic malarious area) and none had been subjected to the possibilities mentioned above

Accurate history-taking is one of the difficulties met with in tropical medical practice, and is not made any easier by the ready suggestibility of the patient In case 1 the history of ingestion of naphthalene mothballs was spontaneously given, in case 2 a doctor's note was available In case 3 the taking of aspirin, phenacetin, and caffeine tablets was verified by asking the patient to pick up the tablets that resembled those taken, from a series of white tablets of various sizes, including phenobarbitone and several sulphonamides

Gross et al (1958) demonstrated glucose-6-phosphate dehydrogenase deficiency in the erythrocytes of patients with hæmolysis following the ingestion of naphthalene They showed this defect to be present in 7 2% of healthy Negroes and in 1 3% of healthy Caucasians Phenacetin is also known to induce hæmolysis in patients with a deficiency of glucose-6-phosphate dehydrogenase (Beutler 1959, Houston and Barlow 1959)

As the incidence of the glucose-6-phosphate dehydrogenase-deficiency trait in Yorubas is about 20%, being present in 61 out of 292 patients examined, one might expect to see in the University College Hospital, Ibadan, a greater number of adults with drug-induced hæmolytic anæmia and hæmoglobinuria than one does The self-limiting nature of the hæmolysis (Beutler 1959) may be one reason for this apparent discrepancy, the hæmoglobinuria ceasing before the patient decides to attend hospital It would be interesting to know how often this complaint is seen in general practice in Ibadan Another reason for the comparative paucity of cases of hæmoglobinuria seen in hospital may be that a critical concentration of the potentially noxious drug is required to induce hæmolysis and that this level varies from individual to individual

The existence of the deficiency trait in Nigeria and in other parts of Africa makes it necessary to test for it in all cases of hæmolytic anæmia exhibiting a negative Coombs test for which no other obvious cause can be found An attempt should be made to elicit an adequate history with particular reference to drugs taken In areas where the epidemiological evidence is strongly against a diagnosis of " blackwater fever ", the presence of this intrinsic erythrocyte defect should be looked for in all adults with hæmoglobinuria The hæmolysis is self-limiting and this should be remembered when assessing new therapeutic measures for hæmolytic anæmia and hæmoglobinuria in areas where the trait is present

Summary

Three cases of hæmoglobinuria in adult Nigerians are described and all are attributed to glucose-6-phosphate dehydrogenase deficiency in the erythrocytes together with drug sensitivity The presence of the trait should be looked for in adult Nigerians with unexplained hæmolytic anæmia with hæmoglobinuria which might otherwise be diagnosed as " blackwater fever "

We are indebted to Dr D G Abrahams and to Dr T W G Kinnear, under whose care these patients were admitted, for allowing us to carry out these investigations We are grateful to Prof B G

Maegraith for advice and encouragement and to Prof A Brown for his interest We wish to thank Mr B G Taylor for technical assistance and the department of hæmatology for the hæmatological investigations

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Addendum

Since the writing of this paper, a further case has been seen in a Nigerian male doctor who had taken a total of 5 4 g of phenacetin in 3 days before the onset of hæmoglobinuria The glucose-6-phosphate dehydrogenase rapid-screening test demonstrated low enzymatic activity The direct Coombs test was negative in all dilutions

THE SURGICAL REMOVAL OF BRANCHIAL SINUS

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BRANCHIAL sinus, or lateral cervical fistula, is uncommon, but because of its unvarying anatomy it is easy to recognise and to treat It probably represents the partial persistence of the second branchial cleft This explanation seems to account for its exact and constant anatomical relationships

The case-history is always the same A child is brought up because of an almost imperceptible blemish in the lower half of the neck close to the anterior border of the sternomastoid (fig 1) As a rule nothing can be felt, but occasionally a small lump is palpable or even visible The blemish, on closer inspection, is seen to be a small orifice in the skin leading to a sinus which passes upwards, backwards, and inwards to the region of the pharyngeal wall. From this orifice there exudes from time to time a little sticky, glairy fluid, with an unpleasant adherent quality It is this characteristic of the fistula that makes the parents press for early treatment The only effective treatment is surgical removal Irradiation and injection are unsuccessful and have some morbidity owing to the complications which they may engender

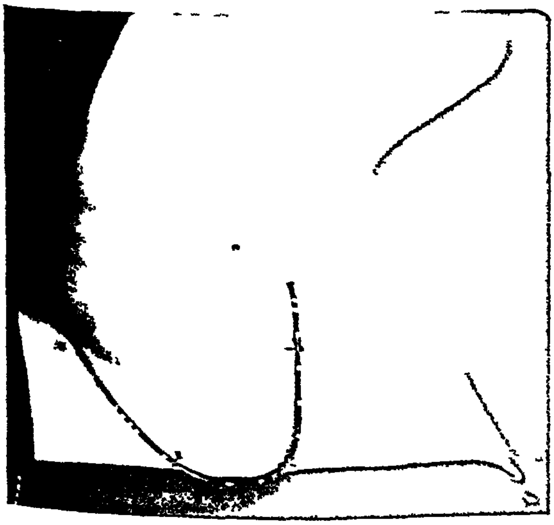

Fig 1—The sinus catheterised

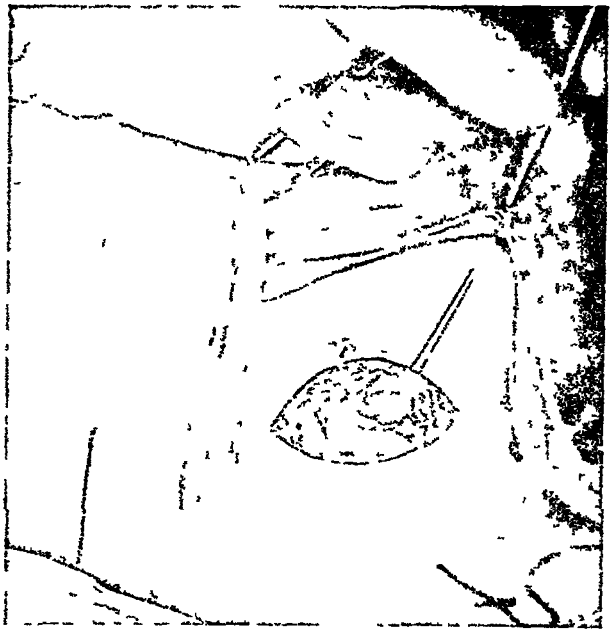

Fig 2—Exposure of the catheterised sinus

The temptation to carry out the operation too early should be resisted The parents can be assured that no complication will result and that no disability will appear during the few years of waiting It can be done in the infant, but it is easier when the child is four or five years old By the age of about four the plump neck of infancy is replaced by the slim neck of childhood, and the dissection is particularly simple and clear

The Operation

The child is given a general anæsthetic and preferably, but not necessarily, intubated He is placed on the table in the thyroid position, with a flat sandbag under the shoulders, and the head fully extended and turned to the side away from the lesion A ureteric catheter, lubricated with 'Vaseline' (not a water-soluble substitute), is passed into the sinus throughout its full length (about 10 to 12 cm at the age of four or five) This catheter is fixed in position by stitching it to the skin as shown in fig 1 No attempt is made at this stage to dissect the lower part of the sinus, but an incision is made in a natural neck-crease with its mid-point overlying the carotid division (fig 2) The internally splinted sinus is identified at a surprisingly short distance beneath the skin (figs 2 and 3) and a ligature is tied round it to reduce movement

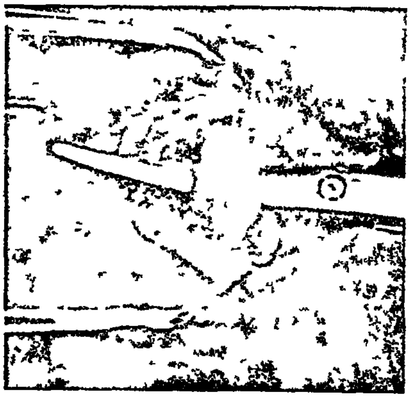

Fig 3—The catheterised sinus
Note the substantial size of the sinus when not attenuated by traction

of the catheter inside it. It lies clearly isolated in, but not of, its environment, and adherent to the surrounding structures only by the lightest of areolar connections The sinus track is large and firm in outline (fig 3). Its lack of intrinsic strength is compensated by the internal splint and its clarity of outline is preserved since it cannot be attenuated by traction A simple blunt dissection frees the sinus in its deepening course, inwards under the hypoglossal nerve, beneath the digastric muscle, between the carotids, over the glossopharyngeal nerve towards the region of the pharyngeal wall

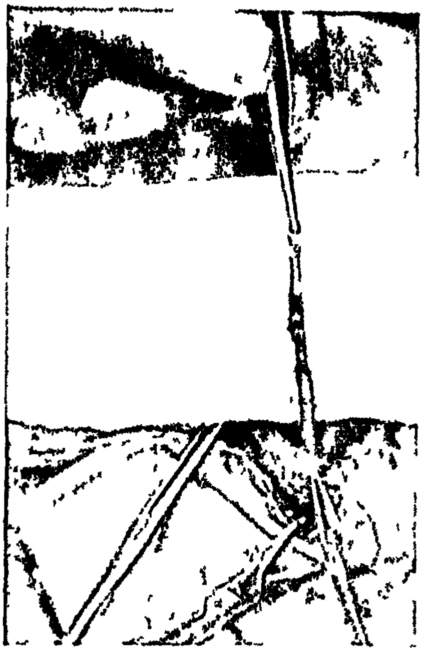

Fig. 4—Upper part of dissection completed.

Is the lesion a fistula or a sinus? It is primarily a sinus Many series have been reported containing a varying proportion of complete fistula—even as many as a third Communications with the pharynx, when they do occur, are possibly due to an embryological accident, but more probably to a pathological or a surgical one In my series of about a dozen cases, I have not encountered a complete fistula nor have I met with an example of the short blind sinus which has been described The considerable variation in estimates of complete fistula is evidence of an accidental rather than an embryological cause

The sinus always, or nearly always, ends blindly and may be dissected free without any interference with, or damage to, the pharyngeal wall (fig 4). König's method, in which a probe is passed from the interior of the pharynx into the tissues of the neck and the sinus, or part of it, dragged into the pharynx, is ingenious but unnecessary

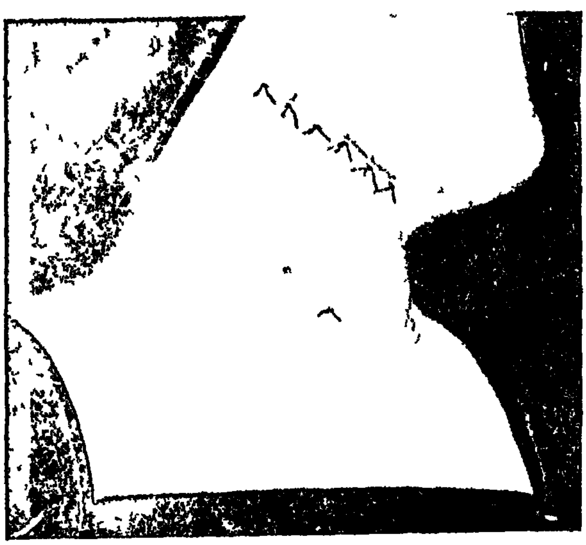

Fig 5—The incision closed

The upper end of the sinus having been freed, the lower portion of the track (a little more adherent than the upper) is separated by blunt dissection from under the lower skin-flap, and the operation is completed by a tiny incision encircling the orifice, through which the track and its splint are withdrawn No attempt should be made to cut a circle but the opening should be freed by two minute transverse cuts while the orifice itself is held up as an apex by a Gillies hook The incision itself and this small slit are sutured and sealed (fig 5) No drain is necessary The operation is usually performed under penicillin cover because of the possibility of damage to the pharyngeal wall, but it is doubtful whether this is really necessary

A somewhat similar approach may be made in dealing with a thyroglossal cyst and its track, though catheterisation as an aid to dissection is not possible The incision is made over the hyoid region rather than over the prominence of the cyst The cyst and lower part of the track are readily freed from under the lower flap, and the higher and more difficult part of the dissection is done from under the upper flap and at close range

PHENYTOIN IN THE TREATMENT OF TRIGEMINAL AND OTHER NEURALGIAS

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Drug therapy in trigeminal neuralgia has not been notably successful The usual analgesics are of limited value, and claims that courses of daily injections of vitamin B_{12} have given relief have not been substantiated In most cases one has to resort to surgical interruption of the pain pathways, and, though usually successful, this is a major procedure in patients who are often old and frail and have other diseases It is not surprising that the therapy of this disorder is unsatisfactory, since little or nothing is known of its ætiology But the special nature of the pain, its paroxysmal quality, and its provocation by peripheral stimulation within the area innervated by the trigeminal nerve, seem to postulate a state of increased excitability leading to maximum response

The analogy with epilepsy which this calls to mind seems close enough to warrant a trial of anti epileptic drugs Experimental evidence suggests that phenytoin (diphenylhydantoin) is capable of reducing nerve excitability (Morrell et al 1958), in addition it has been shown to raise the threshold of the trigger mechanism in trigeminal neuralgia (Kugelberg and Lindblom 1959) Its use in treating trigeminal neuralgia has also been reported in some small series (Berczeller and Szecsody 1956, Kubanyi 1956, Sugar 1959, Iannone et al 1958)

The Trial

In the past 3 years in this clinic we have used phenytoin as a first line of treatment in twenty patients with trigeminal neuralgia

Their ages ranged from 39 to 78 years, most of them being over 60. Their histories varied in length from several months to several years, and all had been treated previously by analgesics, vitamin injections, alcoholisation, or electrotherapy in various combinations All had the typical features of the disease—i.e , lancinating pain, limited to the region of the fifth nerve in one or more of its branches, provoked by cold touch, or chewing—and, except for one case of multiple sclerosis, they had no other signs of disease of the nervous system The patients were each given phenytoin 0 1 g (gr $1^1/_2$) by mouth t i d

Results

Six patients reported complete lack of benefit from phenytoin, and they were subsequently treated by alcohol injections or operation In the remaining fourteen phenytoin was effective, though in variable degree Of these fourteen patients, eight (including the one with multiple sclerosis) reported complete relief In the others improvement was partial in that attacks were not entirely abolished but were less severe and less frequent (e g , 2 or 3 per day instead of 8 or 10 per hour), in these cases the disease was made tolerable, so that eating, drinking, and washing were possible Hence no chemical or surgical attack on the nerve was thought necessary

All the patients helped by phenytoin, either by arrest or mitigation of their attacks, noted improvement in the first 24-48 hours, and occasionally after the first dose The change in their appearance provided striking evidence of the effectiveness of the drug This was particularly rewarding in those patients who had been referred to hospital for surgery, to which they had become resigned, and who had been resentful of being " put off " with yet another trial of drugs

After a few weeks of continuous treatment, the patients were asked to stop taking phenytoin for a trial period, and to start again should the symptoms return In three cases now followed up for 3 years this self-regulated regime has proved satisfactory, giving adequate relief, total or partial, whenever the pains have returned On the other hand, one old lady, after many months of suffering, gained complete relief within 2 days of starting phenytoin, and refused to stop taking the tablets because of fear of a recrudescence of pain, but after 12 months' freedom the symptoms returned, suggesting that habituation had rendered the treatment ineffective

All our patients had had trigeminal neuralgia for months or years before the trial with phenytoin, and they had been treated in various ways, in the successful cases the abolition of symptoms was so striking that there seems to be no reason not to attribute it to the specific therapy At the time this trial was being conducted, some half-dozen patients were seen to whom the label " atypical facial pain " was attached They complained of pain in the face, not strictly within the trigeminal area, and lacking a true paroxysmal character In none of them was phenytoin of any help, whereas tranquillisers and sympathetic attention to personal problems did give some benefit

Phenytoin in other Paroxysmal Neuralgias

The usefulness of phenytoin in trigeminal neuralgia prompted its trial in other painful conditions with paroxysmal features Four patients had symptoms appropriate for this purpose

Two patients were tabetics with lightning pains, who were both helped considerably

In one, success was spectacular This unfortunate man was admitted to hospital directly from the outpatient department in a pitiable condition Several times every minute he was seized with excruciating though momentary pain radiating down his left leg, which made him cry out He isolated himself on the ward terrace in an attempt not to disturb his neighbours He was given phenytoin 0 1 g q i d , on the 2nd day in hospital he no longer shouted with each paroxysm, though he still reported pains when questioned On the 3rd day he was completely free from pain, and his smiles were in gratifying contrast to his previous expression of agonised apprehension After 5 days' treatment, sodium bicarbonate tablets were substituted for the phenytoin without the patient's knowledge Next day the pain returned as before, to his great disappointment, but once again responded to phenytoin within 24 hours

The two other patients had had post-herpetic neuralgia of the thorax for several months Both had two kinds of pain—a constant dull ache, and sudden exacerbations lasting about a minute and recurring many times a day In both patients the paroxysmal attacks were relieved by phenytoin, but the constant ache was unaffected Stopping the therapy was followed by return of the paroxysmal pain

We are not aware of the previous use of phenytoin in these varieties of shooting pain, which are believed to be associated with disease of the posterior-root ganglion, though since our trial we have learnt that this therapeutic approach had been mooted by Prof Wilder Penfield and Dr B Dattner in discussing a paper by Caveness et al (1949) On the basis of the above experience, however, we feel that a wider trial of phenytoin, and perhaps other anticonvulsant drugs, is justifiable in the symptomatic treatment of all varieties of paroxysmal neuralgia

Summary

Twenty cases of trigeminal neuralgia were treated with phenytoin (diphenylhydantoin) Relief of pain was complete in eight, and partial in six The drug had no effect in six

Phenytoin should be tried in every case before a decision is made to embark on alcohol injection or surgical division of the nerve

Phenytoin was also effective in the treatment of lightning pains in two cases of tabes, and of paroxysmal pains in two cases of neuralgia after herpes zoster

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THE EFFECT OF VITAMIN-B_1 THERAPY ON BLOOD-PYRUVATE LEVELS IN SUBACUTE COMBINED DEGENERATION OF THE CORD

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PYRUVATE metabolism is abnormal in some cases of subacute combined degeneration of the cord Earl et al (1953) described raised blood-pyruvate levels in three untreated cases of subacute combined degeneration, which returned towards normal after treatment with crystalline vitamin B_{12}

Joiner et al (1950) had previously found normal pyruvate-levels in six subjects with subacute combined degeneration already under treatment with vitamin B_{12} The inference that an abnormality of pyruvate metabolism is corrected by B_{12} is somewhat surprising because the vitamin believed to be instrumental in the decarboxylation of pyruvic and other keto acids is vitamin B_1 (aneurine, thiamine) There is no evidence that treatment with B_1 has any influence on the course of subacute combined degeneration of the cord

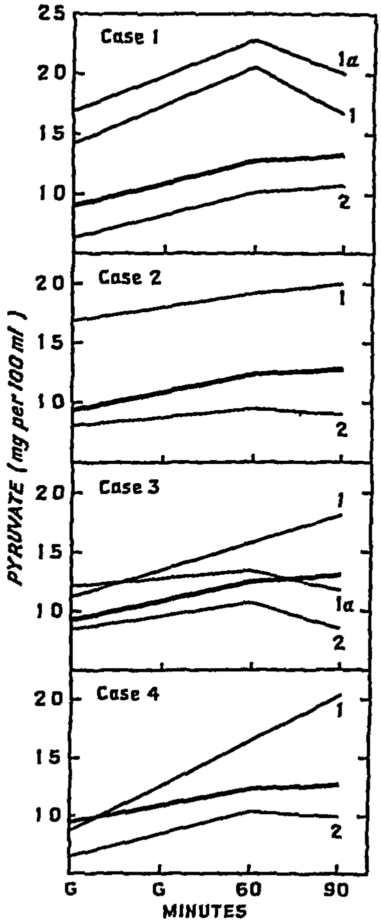
Although the metabolic relationship of vitamin B_{12} to the functioning of the central nervous system is still unknown, it has been shown that the clinical manifestations of subacute combined degeneration of the cord respond only to B_{12} (Jukes 1952) It may be that the lack of B_{12} sets in train disturbances of metabolism outside the field of its direct action It seemed of interest, therefore, to determine whether the administration of B_1 without B_{12} would correct the pyruvate disturbance

A number of untreated cases of subacute combined degeneration have now been studied in the National Hospital and the effect of large amounts of B_1 on the blood-pyruvate levels has been observed

Method

On admission blood-pyruvate levels were measured, by the method of Friedemann and Haugen (1943), first while fasting, and then 60 and 90 minutes after the ingestion of glucose. *Two doses of 50 g of glucose in 200 ml of water were given,* one at the beginning of the test and the other 30 minutes later, as described by Joiner et al (1950)

The test was repeated after a course of B_1 100 mg had been given intramuscularly daily for 10–16 days, this technique was used by Joiner et al, when comparing the effect of B_1 and dimercaprol (B A L) on the abnormal pyruvate metabolism of peripheral neuropathy Serum-B_{12} levels were measured by Dr L Mollin of the Hammersmith Hospital, London



Effect of treatment with vitamin B_1, 100 mg intramuscularly given daily, upon blood-pyruvate levels after 100 g glucose in divided doses by mouth, in four patients with subacute combined degeneration of the cord

At G 50 g of glucose were given, curve 1—before commencing treatment, curve 1a—after 2 days' treatment, curve 2—after 10–16 days' treatment The upper limit of normal is shown for comparison

Case-records

THE FIRST CASE

A 65-year-old man was admitted [N H 81819] in November, 1958, complaining of weakness of the legs, which had gradually increased over the preceding 12 months He was pale and had a smooth red tongue There was no change in muscular tone in the lower extremities, but there was weakness of the hip flexors and the dorsiflexors of the feet Coordination was severely impaired in the lower limbs, and there was a marked disturbance of position sense in the toes and ankles The knee and ankle jerks were absent, but the plantar responses were extensor

Investigations

There was a histamine-fast achlorhydria Hæmoglobin 13 6 g per 100 ml , red-cell count 4,420,000 per c mm., colour index 1 0 Sternal bone-marrow, megaloblastic erythropoiesis typical of pernicious anæmia Serum-B_{12}, 53 μg per ml (normal range 200–320 μg per ml)

Treatment with B_1 100 mg twice daily by intramuscular injection was started on Nov 19, after which there was no neurological improvement On Nov 30, B_{12} was given, 1000 μg daily for a week, and then at weekly intervals Improvement followed this treatment, the hæmoglobin rose to 15 g per 100 ml , and the strength and coordination of the lower limbs gradually increased The results of the pyruvate metabolism tests are shown in the figure (case 1)

THE SECOND CASE

A man, aged 62, was admitted [N H 71035] in February, 1957, with a history of attacks of vertigo for 12 months and cramps in the fingers for 6 weeks 6 years previously a gastrectomy for a gastric ulcer had been performed

He looked pale and thin There was some nystagmus on lateral deviation of the eyes, and a generalised muscular weakness with a peripheral loss of cutaneous sensation was present in the hands and feet The deep reflexes were all present, and the plantar responses were extensor

Investigations

Hæmoglobin 11 3 g per 100 ml , red-cell count 2,900,000 per c mm , colour-index 1 3 There was poikilocytosis and macrocytosis, and the sternal bone-marrow showed megaloblastic erythropoiesis There was a histamine-fast achlorhydria

Treatment with B_1 100 mg daily was begun on March 21, 1957 There was no objective change in his condition and, on April 9, vitamin B_{12} 1000 μg was given daily for one week, and then at weekly intervals After this regime the blood-counts improved rapidly but neurological improvement was slow The results of pyruvate metabolism tests are shown in figure (case 2)

THE THIRD CASE

A 52-year-old married woman experienced numbness of both legs for 18 months, and pins-and-needles in the fingers for 6 months

She was depressed, the skin was pale, and the hair grey Muscular tone was decreased in the legs, the deep reflexes were brisk, except at the ankles where they were sluggish, the plantar responses were extensor There was impairment of cutaneous sensation on the legs, extending up the trunk to the 10th thoracic dermatome, and on the arms below the elbows Postural sense was impaired at the ankles and toes She was admitted [N H 70159] for further investigations

Investigations

Hæmoglobin 12 2 g per 100 ml , red cell-count 3,700,000 per c mm , with macrocytosis and poikilocytosis Colour-index 1 1 The sternal bone-marrow showed megaloblastic changes There was a histamine-fast achlorhydria

Treatment with B_1 100 mg intramuscularly daily was begun on June 25, 1957, and continued for 2 weeks The administration of B_{12} 1000 μg daily, and later at weekly intervals, has been followed by improvement in the blood-count Neurological recovery has been incomplete although some improvement has taken place The results of the pyruvate-metabolism test are shown in figure (case 3)

THE FOURTH CASE

A man, 68 years old, complained of pins-and-needles in the feet for 2 years, with an unsteady gait for 6 months A gastrectomy had been performed for gastric ulcer 15 years before

The skin was pale, the hair white There was no increase in muscular tone, but coordination was impaired in the legs The knee-jerks were brisk, but the ankle-jerks were absent, the plantar responses were extensor Postural sensation was impaired in the toes and slight cutaneous sensory loss was present in the lower third of the legs He was admitted [N H 79473] for further investigations

Investigations

Hæmoglobin 7 7 g per 100 ml, red-cell count 3,970,000 per c.mm Colour-index 0 67 There was hypochromia and anisocytosis The sternal marrow was normal A histamine-fast achlorhydria was present The serum-B_{12} concentration on two occasions was 35 µg per ml and 5 µg per ml

Treatment with B_1 100 mg daily was begun on June 25, 1958 No clinical improvement occurred and on July 9 B_{12} was given with subsequent neurological and hæmatological improvement The results of the pyruvate metabolism tests are shown in figure (case 4)

Discussion

Although the observations are few, the results of this study appear to confirm the presence of an elevated pyruvic acid in the serum in some untreated cases of clinical subacute combined degeneration of the cord

This abnormality was corrected by large doses of vitamin B_1 in the four cases studied Earl et al (1953) showed that an improvement in pyruvate metabolism could also be produced by treatment with vitamin B_{12} and they concluded that it played an active part in the oxidation of pyruvic acid

In B_{12}-depletion in laboratory animals, Chang et al (1958) showed an impaired ability to metabolise pyruvic and lactic acid, which was restored to normal by B_{12} therapy They suggested that in B_{12} deficiency a number of alterations might exist in biochemical systems utilising co-enzyme 1 and co-enzyme A, both of which are required for the complete breakdown of pyruvate to carbon dioxide and water through the Krebs tricarboxylic-acid cycle

Details of the exact biochemical role of vitamin B_{12} are still obscure, although the generally accepted view is that it is involved in protein synthesis and may be a co-factor in the incorporation of aminoacids into the protein molecule (Broquist 1958, Smith 1958)

It is possible that in the presence of a deficiency of B_{12} the synthesis of proteins active in oxidation may be defective and consequently pyruvic acid may accumulate in the tissues Joiner et al (1950) pointed out that a number of toxic agents which interact with the protein component of the enzyme system can bring about a biochemical lesion resembling vitamin-B_1 deficiency These authors considered that arsenic produced an abnormal pyruvate-metabolism test in this way They found, however, that in some cases of peripheral neuritis with abnormal pyruvate metabolism, even treatment with massive doses of B_1 had no effect on the serum-pyruvate levels, thus their findings are not in accord with our observations in which B_1 has been shown to be effective

A real or relative lack of B_1 may occur in subacute combined degeneration of the cord

Goodhart and Sinclair (1940) found low values of cocarboxylase in three out of six patients suffering from subacute combined degeneration of the cord, similar levels were found in pernicious anæmia without cord involvement They believed that poor dietary habits and gastrointestinal dysfunction were responsible for a vitamin-B_1 deficiency in this condition Though they agreed that there was no evidence that B_1 played any part in causing the cord lesions of subacute combined degeneration, they suggested that it might play a part in the ætiology of the peripheral neuritis They found some in-vitro evidence that B_1 was inactivated in the stomach of patients with achlorhydria (Sinclair 1939) Melnick et al (1941) were unable to confirm this observation but they did show that bile inactivated B_1 in the stomach and that an acid pH had some protective action

Cayer et al (1946) described a reduction in the levels of B_1, nicotinic acid, and riboflavine in pernicious anæmia resembling that found in deficiency states They suggested that deficiencies of these vitamins might account for some of the clinical features observed in pernicious anæmia and for their improvement after multiple vitamin-replacement therapy

It is interesting that two of these cases had previously had partial gastrectomies for peptic ulcer Richmond and Davidson (1958) have drawn attention to neurological disease arising as a consequence of gastric operations, fistulæ, and other anatomical lesions of the small bowel They emphasise the rarity of such cases However, patients who have a defect of the stomach or small bowel associated with malabsorption are more liable to multiple deficiencies Nicol (1960) demonstrated malabsorption of several vitamins in a case of non-Addisonian megaloblastic anæmia

The improvement in pyruvate metabolism found in subacute combined degeneration of the cord is a manifestation of many complex metabolic processes and may have several mechanisms in its production The chemical abnormality observed can be corrected by both vitamin B_1 and vitamin B_{12}, and although these two vitamins may produce their effect through a single channel this need not be so

It is tempting to suggest, however, that the peripheral neuropathy of subacute combined degeneration is precipitated by a B_1 lack and that its improvement with treatment with B_{12} is due to such secondary factors as altered nutrition and improved absorption of B_1

Alternatively the relatively large amounts of B_1 may permit the utilisation of an alternate metabolic pathway which, while adequate for the disposal of pyruvate, is unable to replace B_{12} in protein metabolism A comparable effect is that of large doses of folic acid on the hæmatological abnormality of pernicious anæmia though the fundamental metabolic block remains undisturbed

Summary

Raised blood-pyruvate levels were found in four untreated cases of subacute combined degeneration of the cord, and were restored to normal by treatment with crystalline vitamin B_1 100 mg daily (aneurine, thiamine) It is suggested that in some cases of subacute combined degeneration a deficiency of both vitamins B_1 and B_{12} (cyanocobalamin) is present which may be the result of malabsorption from the gut

We wish to thank Dr J Marshall and Prof J N Cumings for encouragement and advice, Dr Denis Williams and Dr J St C Elkington for permission to study and report their cases, and the medical committee of the National Hospital for permission to publish this paper

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CHEMICAL SPLENECTOMY

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RECENT developments in the chemical control of reticuloendothelial phagocytic function (Stuart et al 1960) have shown that certain simple fatty molecules exert a profound effect on the sessile cells which remove particulate matter from the blood-stream During the investigation of a further series of compounds it was noted that colloidal preparations of ethyl palmitate (' Ethpalm ') given intravenously caused not only suppression of phagocytic function but also widespread necrosis of the spleen

Material and Methods

A colloidal preparation of 10% ethyl palmitate was made by homogenisation, and injected into mice in a dose of 25 mg of ester per 20 g body-weight Twenty-four hours later the reticuloendothelial phagocytic function was measured by the carbon-clearance technique (Biozzi et al 1957) Colloidal carbon was injected intravenously in a dose of 8 mg per 100 g body-weight

The rate of clearance from the blood follows an experimental function according to the equation $\frac{\log C_1-\log C_2}{T_2-T_1}=K$ where C=the concentration of carbon in the blood at time T, and K is the phagocytic index.

At the end of the experiment the animals were killed and paraffin sections were made of spleen, liver, bone-marrow, and thymus

Results

The value of K for the control mice was 0 05, and in the treated mice it was 0 009 Microscopic examination of the spleen (fig 1) shows widespread destructive changes which affect both pulp and malpighian bodies The pulp is acellular and œdematous The surviving cells show considerable nuclear changes, comprising pyknosis, intranuclear vacuolation, and loss of usual staining properties The giant cells of the spleen are also damaged and their lobular nuclei are distorted into black skeins of chromatin The malpighian bodies are more resistant, the early lesions consist of necrosis of peripheral lymphoid cells (fig 2), which may proceed to total loss of lymphoid cells, leaving only a central arteriole surrounded by isolated and dead lymphocytes Silver impregnation methods reveal total fracture of the reticulin framework.

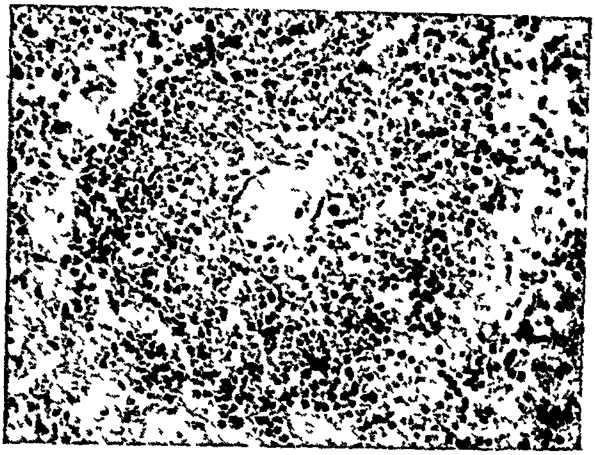

Fig 2—Spleen after treatment with ethpalm showing dissolution of a malpighian body (H & E × 250)

Sections of bone-marrow, thymus, and liver show no significant lesions, although in one case a few minor foci of coagulative necrosis were seen in the liver

Discussion

The phagocytic index, K, is profoundly reduced in treated animals, and the likely explanation is suppression of functional activity in all reticuloendothelial cells which are in contact with the blood-stream Since the liver fixes much more of the carbon than the spleen, it seems unlikely that the splenic necrosis is responsible for the diminished phagocytic function, a view supported by the microscopic finding in ethpalm-treated animals of fewer carbon-containing cells in the liver

The distribution and fate of ethpalm within the tissues is unknown, but, because of its particulate nature, it is probably selectively removed by the Kupffer cells of the liver and also by splenic and bone-marrow histiocytes

The curious affinity of ethpalm for the spleen apparently supports the theory of regional differences of reticuloendothelial function This is not necessarily true since the physicochemical properties of the compound effectively prevent (at the moment) its passage through the capillary barrier, and accordingly inhibit entry to lymph-glands and thymus We know that the liver phagocytes are affected because of the low values of the phagocytic index, and the relative absence of liver damage is presumably due to efficient " detoxication " by the parenchyma It seems probable that the mechanism of action is related to a critical concentration of ethpalm within phagocytes, which is followed by cell damage and release of cytotoxic material into the susceptible lymphoid tissue of the spleen This theory is supported by my experimental finding that minute doses of ethpalm inhibit only phagocytic function whereas larger amounts are required to produce the

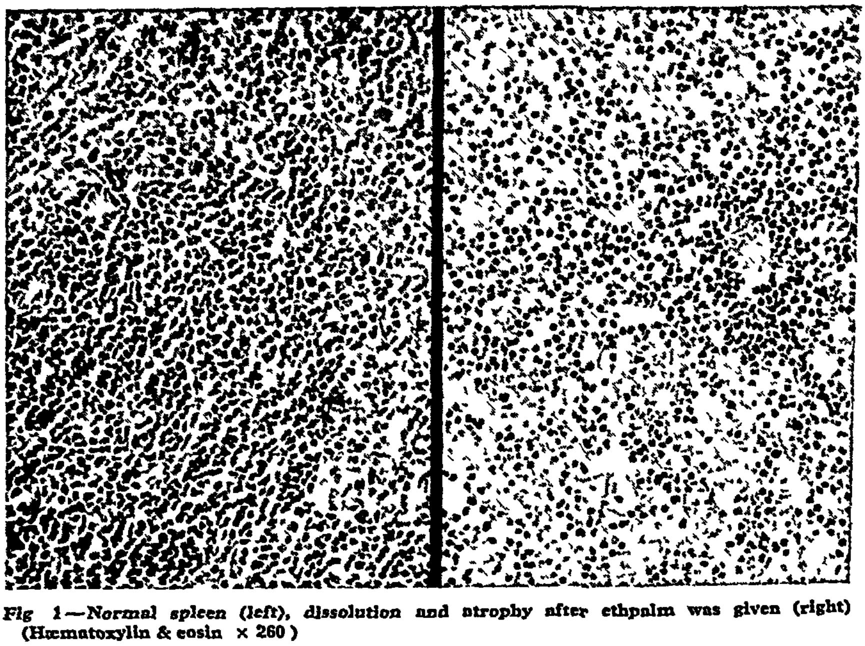

Fig 1—Normal spleen (left), dissolution and atrophy after ethpalm was given (right) (Hæmatoxylin & eosin × 260)

findings described here Furthermore, the bone-marrow has but few phagocytes, and the absence of damage to that organ is explained by inability to store an adequate concentration of the compound

Various colloidal materials have been used in the past for destruction of lymphatic tissue Finely divided silica is a well-known example, and colloidal gold has produced severe lesions (Hahn et al. 1956) Emulsified lipids, given in large doses by the intraperitoneal route, have resulted in regional lymph-node destruction (Shivas and Fraser 1959) Ethpalm, which differs from these agents in that a relatively small dose is required, is the only one of several related compounds which produces this striking and selective effect. Accordingly its molecular structure must be intimately associated with the biological effect, which may prove a useful instrument for control of splenic function.

Summary

Ethyl palmitate administered intravenously suppresses phagocytic function and causes destruction of the spleen. The bone-marrow and lymphoid tissue of the thymus are unaffected.

I am indebted to Prof G L Montgomery for helpful criticism, to Mr H Drysdale, final year medical student, for invaluable technical aid, and to Mr T C Dodds for the photomicrographs

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"IDIOHYPOPHYSEAL" DIABETES MELLITUS IN TWO HYPOPHYSECTOMISED WOMEN

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Administration of large doses of growth hormone (G.H.) to adult animals of some species produces a clinical picture similar to that of diabetes mellitus, which disappears when the administration is stopped (idiohypophyseal diabetes mellitus) Prolonged administration of large doses of G.H. to these animals produces diabetes mellitus which persists even after the administration of G.H. is discontinued (metahypophyseal diabetes mellitus) (see Young 1953, Astwood 1955, Ketterer et al 1957, de Bodo and Altszuler 1957, and Young and Korner 1960)

Administration of human growth hormone (H.G.H.) in small to moderate doses—1–10 mg, or 17–170 µg per kg body-weight, daily—to hypophysectomised adult patients with juvenile diabetes mellitus produced within hours a pronounced deterioration of the diabetic condition leading to severe acidosis (Luft et al 1958, 1959, Greenberg et al. 1958, Dominguez et al. 1960) In hypophysectomised patients with adult-type diabetes H G H in daily doses of 5 to 10 mg daily (90–170 µg per kg) for several days induced hyperglycæmia, glycosuria, and ketonuria without significant change in acid-base balance (Dominguez et al 1960) Similar results have been observed in non-hypophysectomised patients with diabetes mellitus given 5–30 mg of H G H daily (90–510 µg per kg) for a few days irrespective of the type of diabetes (Ikkos and Luft 1960, Hennemann and Hennemann 1960)

A decrease in glucose tolerance has been observed in a pituitary dwarf given large doses (440 µg per kg daily) of H G H (Beck et al. 1957) and in subjects with hypopituitarism on cortisone replacement therapy given H G.H. in doses of from 200 to 600 µg per kg daily (Ikkos et al. 1959, Beck et al. 1960) In a pituitary dwarf 5–10 mg daily of H.G.H. initially resulted in a decrease in glucose tolerance but later this returned to normal (Escamilla et al. 1960) Smaller doses of H.G.H (30–150 µg per kg daily) had little or no effect on the fasting glucose concentration of a hypopituitary subject (Greenberg et al 1958)

The effects of H.G.H on the carbohydrate metabolism of subjects with normal pituitary function have generally been less pronounced. Doses of 170 to 510 µg daily have induced a decrease in the glucose tolerance of some such subjects (Ikkos and Luft 1960, Ikkos et al. 1959), while smaller doses (30–150 µg daily) had no or little effect on blood-glucose concentration and glucose tolerance (Greenberg et al 1958, Escamilla et al. 1960)

From the above data it is obvious that H G H. by and large has the same effects on glucose metabolism as those previously described in laboratory animals On the other hand, idiohypophyseal diabetes mellitus in man has not yet been reported. It was therefore considered worth while to present two such instances observed in hypophysectomised non-diabetic females

Material

Both patients had been previously hypophysectomised because of metastatic breast cancer Both volunteered for the present study, the nature of which was explained to them. Their general condition was excellent at the time of the present study, and cancer growth was limited. The past medical history of case 1, aged 46, was negative. Case 2, aged 62, had been obese for many years, her weight was 100 kg (15 st. 10 lb), height 168 cm. (5 ft. 6 in.) There was no history of diabetes mellitus in the patients or their families, and routine blood-sugar determinations and urinanalysis were normal. Both patients received adequate thyroid replacement therapy, their daily cortisone substitution is seen in table I

Methods

The patients were admitted to hospital in July, 1960, for studies of the effect of H.G.H. on carbohydrate metabolism. They received a constant diet providing 1700 calories daily, composed of 80 g of protein, 270 g of carbohydrate, and

TABLE I—EFFECTS OF HUMAN GROWTH HORMONE

Day of study	Cortisone acetate (mg per day)	H.G.H. (mg. per day)	Fasting blood-glucose* (mg. per 100 ml.)	Glucose in urine (g per day)	Ketone bodies in urine	Nitrogen in urine (g. per day)	K value**
Case 1							
1	37·5			0	–	10·3	
2	37·5			0	–	8·4	
3	37·5	20 †	72 ‡	0	–	7·9	1·35
4	37·5	20 †		1	++	3·0	
5	37·5	20 †	98 ‡	5	+++	4·0	0·59
6	37·5		109 ‡	11	–	4·8	0·73
Case 2							
1	50			0	–	14·4	
2	50			0	–	13·1	
3	50	20 †	82 ‡	0	–	13·9	0·71
4	50	20 †	134	21	+	6·8	
5	200 ¶		153 ‡ (269) §	86	++	6·9	0·31
6	100 ¶		91	16	–		

* Glucose-oxidase method of Middleton and Griffiths (1957)
† Given intramuscularly as a single dose at 5 P.M.
‡ Mean value of 15 determinations between 7 and 9 A.M.
§ Blood-glucose concentration at 6 P.M.
¶ 25 mg at 7 A.M. and 1 P.M. 100 mg at 6 P.M., and 50 mg at midnight. 50 mg at 7 A.M. and 7 P.M.
** Rate of disappearance of glucose (in per cent. per min.) calculated from an intravenous glucose-tolerance test according to Ikkos and Luft (1957)

fat Urinary nitrogen, glucose, and ketone bodies were measured daily 20 mg of H G H was given intramuscularly daily for three days in case 1 and for two days in case 2 The preparation used was prepared by Dr C H Li, of Berkeley, California The H G H was dissolved in 10 ml of physiologic saline immediately before injection, pH was adjusted to approximately 9 5 with a few drops of 0 1 *N* NaOH Increased amounts of cortisone had to be given to case 2 on days 5 and 6 because of incipient adrenal crisis—i e, nausea, anorexia, pronounced tiredness, and tachycardia (110 per minute) on days 4 and 5, and fever of 38 4°C (100 4°F) on the afternoon of day 5 These symptoms were quickly ameliorated by cortisone

Results and Discussion

The effects of H G H on fasting blood-glucose, glycosuria, and ketonuria are summarised in table I In both patients there was an increase in fasting blood-glucose during H G H administration, and glycosuria and ketonuria appeared Furthermore, the intravenous glucose-tolerance test showed a decrease in glucose tolerance In both cases the rate of disappearance of glucose — "k" value (table I)—decreased during H G H Nitrogen excretion in the urine decreased notably in both cases despite the appearance of glycosuria These changes are analogous to those of idiohypophyseal diabetes mellitus in laboratory animals, where the characteristic features are nitrogen retention during the development of the diabetic state The diabetic state produced in such animals was generally more pronounced than in this study It should be noted, however, that the doses of growth hormone used in dogs and cats (about 3 mg per kg daily) are much larger than those given in the present study (0 3 and 0 2 mg per kg daily)

The response of both patients to H G H, although qualitatively similar, differed in magnitude, being more pronounced in case 2 It has been reported that in some species glucocorticoids act synergistically with growth hormone in the production of diabetes mellitus (Ketterer et al 1957) It might therefore be wondered whether the extra cortisone given to case 2 on day 5 was responsible for the difference mentioned above However, the presence in case 2 of glycosuria on day 4 and hyperglycæmia on days 4 and 5, before extra cortisone was necessary, demonstrates that even in this patient an excessive amount of cortisone was not a prerequisite for the diabetogenic action of H G H

TABLE II—PARAMETERS OF GLUCOSE METABOLISM

—	Case 1			Case 2	
	Day 3 *	Day 5	Day 6	Day 3 *	Day 5
I Fasting conc of glucose in plasma water † (mg per 100 ml.)	86 4	117 6 (+36)‡	130 8 (+51)	98 4	183 6 (+87)
II Glucose pool§(g)	15 1	20 6 (+36)	22 9 (+52)	24 6	45 9 (+87)
III Turnover-rate of glucose (% per min)	1 37	0 73 (−47)	0 74 (−46)	0 76	0 51 (−33)
IV Glucose inflow and outflow ¶ (mg per min)	207	150 (−28)	169 (−18)	187	234 (+25)
V Total $^{14}CO_2$ activity expired during 0–120 min ‖ (counts per min)	1 87 × 10^6	1 56 × 10^6	1 38 × 10^6	1 76 + 10^6	1 30 × 10^6
VI Glucose metabolised to CO_2 during 0–120 min **	28 2 × 10^6	32 1 × 10^6 (+13)	31 6 × 10^6 (+12)	43 3 × 10^6	59 7 × 10^6 (+38)

* Control day

† Calculated from whole blood glucose measured by glucose-oxidase method of Middleton and Griffiths (1957), water content of blood taken as 83%, blood-glucose measured in 12–14 samples taken between 7 and 9 A M

‡ Values in parentheses represent the difference between the values for experimental and control days in per cent of the control values

§ Product of values in row I and the volume of distribution of glucose (taken as 25% of body-weight)

¶ Product of values in rows II and III

‖ Identical amounts of ^{14}C glucose were given in successive tests in each patient.

** Product of values in rows II and V

Using uniformly ^{14}C-labelled glucose (New England Nuclear Corp, 0 1 mC per 47 6 mg glucose), glucose turnover studies were performed in the postabsorptive state before and after H G H 25 µC of ^{14}C-labelled glucose was given in a single intravenous injection, and venous blood samples were thereafter collected every 10 minutes between 30 and 120 minutes Measurements of blood-glucose and of total ^{14}C activity of a 1 10 Somogyi filtrate of whole blood were performed on all samples The total amount of expired CO_2 as well as the total ^{14}C activity in the expired air were also measured during the period 0–120 minutes Details of the technique and measurements will appear elsewhere Preliminary results of these studies are shown in table II

The glucose pool increased in both cases as a result of the increase in the fasting glucose concentration On the other hand the turnover-rate of glucose,* calculated from the change in ^{14}C activity of whole blood, decreased in parallel with the decrease in glucose tolerance (table I) In spite of this, only minor changes were observed in the glucose inflow, since the effect of the decrease in turnover-rate on the glucose inflow was compensated by the increase in the glucose pool In case 1 the glucose inflow decreased by 28% on day 5 and by 18% on day 6, while an increase of 25% was observed in case 2 These findings suggest that the glucose output of the liver was most probably not changed significantly by H G H The blood-glucose concentration remained unchanged during the 2-hour periods of ^{14}C measurements Therefore, the inflow values also represent glucose outflow from the glucose pool Consequently, it seems that the peripheral metabolisation of glucose was not significantly altered by H G H This opinion is supported by the findings with ^{14}C in the expired air Since the amount of ^{14}C glucose given in successive tests was identical, the product of the total amount of expired ^{14}C and the glucose pool can be used as a parameter of the amount of glucose metabolised to CO_2 during the test The values in row VI of table II, calculated as mentioned, demonstrate only small changes of this parameter Thus, these studies did not demonstrate any large changes in the absolute amounts of glucose produced by the liver or utilised peripherally during H G H treatment

Summary

Administration of human growth hormone in a daily dose of 20 mg for two and three days to each of two hypophysectomised non-diabetic patients induced a condition similar to that described as idiohypophyseal diabetes mellitus in laboratory animals

Both patients presented an increase in the fasting blood-sugar and glycosuria simultaneous to a pronounced nitrogen retention Glucose turnover studies by means of ^{14}C-labelled glucose revealed only small changes in the absolute amounts of glucose produced by the liver or metabolised peripherally

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* It has been found (unpublished observations) that the turnover-rate of glucose, calculated from total ^{14}C activity of blood filtrate, shows only minor differences from the one calculated from ^{14}C-activity of glucose See also Berson et al (1959)

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A CHILD WITH 49 CHROMOSOMES

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NON-DISJUNCTION at one of the meiotic divisions during parental gametogenesis is generally considered the most likely origin of aneuploidy of the human somatic chromosome complement

A peculiar form of aneuploidy (trisomy for chromosome no 21, and sex chromosomes of the XXY type) results in a phenotype exhibiting both mongolism and the Klinefelter syndrome (Ford et al 1959, Lanman et al 1960, Lehmann and Forssman 1960) Two instances of double abnormalities, apparently consisting of trisomy for chromosome no 21 and monosomy for chromosomes no 16 and no 12 respectively, are reported by Book (1960) in two mongol patients

In this paper we report a case in which cultured mitotic somatic cells displayed a complement of 49 chromosomes This number is apparently due to trisomy for two different autosomes, together with sex chromosomes of the XXY type

Case-record

A.B , a boy, aged 7 His mother and father, both born in Estonia, are healthy They were 23 and 29 years old respectively at his birth The only sibling, a 1-year-old brother, is healthy A B was delivered after an uneventful pregnancy The birth weight was 2400 g ($5^1/_4$ lb) Malformed external genitalia and evidence of congenital heart-disease were noted during the first days of life He had cyanotic attacks which later ceased

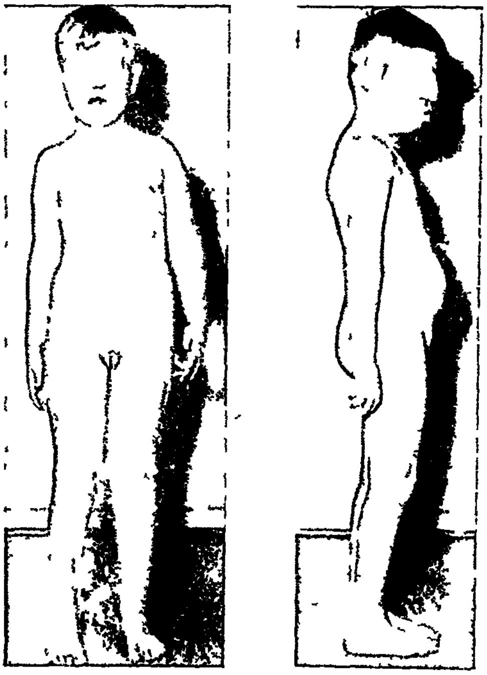
Fig 1a, 1b—Appearance of the patient.

A.B had a flat occiput, epicanthic eye-folds, and a protruding abdomen (figs 1a, 1b) The scrotum was underdeveloped and divided In the middle there was a penis with a central urethral opening (fig 2) A pea-sized mass was palpable in each side of the scrotum No prostate or other internal genitalia were palpable per rectum There was a loud systolic murmur with its maximum intensity at the apex, and another loud, quasicontinuous, systolic murmur at the aortic ostium Subsequently a typical ductus arteriosus of medium size was diagnosed The blood-pressure was 105/70 mm Hg He appeared to be mentally retarded but the mental status has not yet been determined accurately

Clinical Investigations

Hormone determinations (Dr E Diczfalusy) —Total urinary gonadotrophins 6 5 mouse units per 24 hours Urinary œstrogens 10 mouse units per 24 hours

Blood —Cholesterol 200 mg per 100 ml Serum protein-bound iodine 5 5 µg per 100 ml Drumsticks present in neutrophils The blood-groups are being investigated

X-ray examinations —The heart was moderately enlarged Skeleton the ossification centres of the multangulum minus and of the capitulum radii were missing The iliac index was 75°, a value within the normal range (Caffey and Ross 1956)

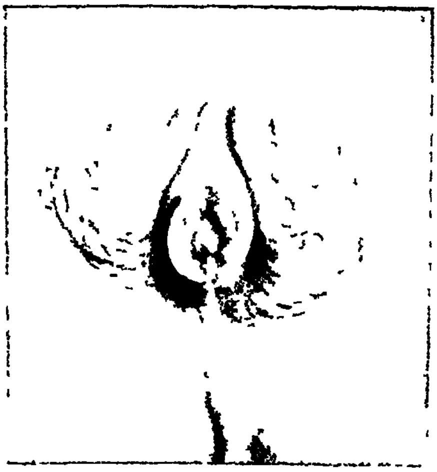
Fig 2—External genitalia

Urography —The contrast medium was well visualised On the right side the renal pelvis was enlarged and the middle portion of the ureter dilated The findings were interpreted as an evidence of slight malformation

Gonad Biopsy

The right groin contained two ovoid struc-

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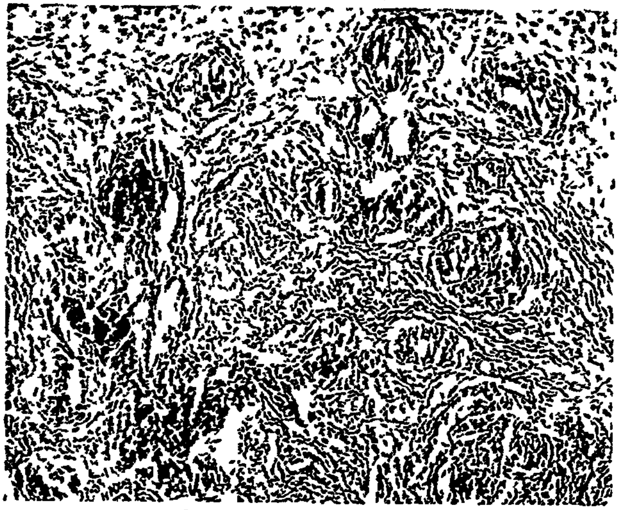

Fig 3—Low-power view of the testis

tures, one (10×8 mm) judged to be a testis and the other an epididymis with a vas deferens Microscopic examination confirmed this

The testis (fig 3) was enclosed by a thickened albuginea and almost structureless Within a wavy connective-tissue stroma there were a few remaining seminiferous tubules containing undifferentiated cells which resembled prepuberal Sertoli cells No cells of the spermatogenic series were present Other tubules were completely obliterated by connective-tissue cells No Leydig cells were observed The blood-vessels showed intimal thickening The epididymal tissue (fig 4) consisted of a rich connective-tissue stroma in which sections of the epididymal canal were observed

Cytological Observations

Bone-marrow and skin biopsies were obtained from A B and his mother, a bone-marrow specimen from his father, and a skin biopsy from his brother The cells were cultured in vitro and handled according to the technique of Fraccaro et al (1960a) Three independent cultures from each biopsy were prepared

Sex chromatin—Cultured cells were stained with basic fuchsin (Feulgen's reagent) and light green (Fraccaro and Lindsten 1959) The interphase nuclei were sex-chromatin positive in A B and the mother, and sex-chromatin negative in the father and the brother

We have made a very detailed study of the sex-chromatin in the cells cultured in vitro This is an efficient method for the study of the Barr-body, since the cells, flattened on the glass surface and stained with a double stain (Feulgen and light green), reveal in great detail the structure of the resting nucleus The cells of the patient were uniformly sex-chromatin positive, thus confirming the probable presence of two Xs No double Barr-bodies were observed nor Barr-bodies of unusual size Having seen this, we thought it unnecessary to investigate the buccal-mucosa smears

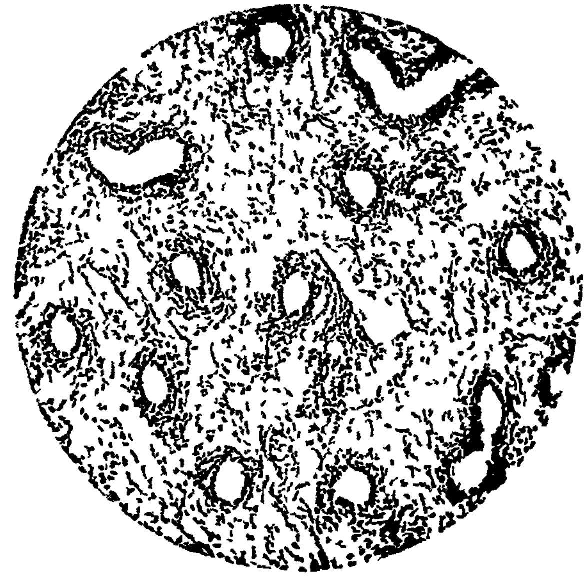

Fig 4—Low-power view of the epididymis

Chromosome number—Chromosome counts were performed on both primary and transferred cultures The results are summarised in the accompanying table The chromosome number was 49 in A B and 46 in his father, mother, and brother

Karyotype of A B

The determination of the karyotype was based on the microscopic examination of more than 70 mitotic cells and detailed analysis of 12 cells by the study of enlarged photomicrographs

Terminology and numeration are according to the standard system of nomenclature (*Lancet* 1960a)

It was possible to separate from the group 6–12 two chromosomes which were interpreted as X chromosomes

The group 6–12 consisted of 16 medium-sized chromosomes instead of the usual 14, and the group 21–22 consisted of the 5 short acrocentric chromosomes observed in normal male cells

THE RESULT OF CHROMOSOME COUNTS

—	Type of culture	Chromosome count ≤43	44	45	46	47	48	49	51	98	Total
A B	Bone-marrow										
	Primary						3	10	1		14
	1st transfer							7		1	8
	2nd transfer						1	7		1	9
	Skin										
	1st transfer							19			19
	2nd transfer						1	15			16
	3rd transfer						1	10			11
Father	Bone-marrow										
	Primary	2	3		18						23
Mother	Bone-marrow										
	Primary	2	1		16	2					21
	Skin										
	Primary	1			2						3
Brother	Skin										
	Primary				7						7
	1st transfer	1	1	1	11						14

By visual inspection it was possible to compose either two trisomics or an extra pair with the two "extra" chromosomes of group 6–12 Chromosome measurements, however, favoured the first interpretation and by the criteria of total length and arm-ratio it was tentatively concluded that there was trisomy for chromosomes no 8 and no 11

Measurements of the short acrocentric chromosomes were less conclusive.

It was possible in every cell to separate, within the 5 acrocentrics, one longer chromosome and label it as the Y chromosome, but the difference in total length between this and the next longest was never significant

In our experience with normal material (Fraccaro and Lindsten 1960) the Y chromosome is generally recognised with relative ease, while in this case a good deal of doubt remained whether there was a Y chromosome or a trisomy for no 21 Many cytogeneticists believe that the Y chromosome may vary in length, even if this impression has not yet been rigorously tested

Against the hypothesis of trisomy for no 21 must be set the failure to recognise with certainty the presence of the 3 satellited short acrocentric chromosomes generally observed in cases of trisomy for no 21 (Böök et al 1959)

We finally decided that the sex chromosomes were probably of the XXY type, and in fig 5 they are placed according to this interpretation

Karyotypes of the Father, Mother, and Brother of A B

All evidence indicated apparently normal karyotypes in these three people

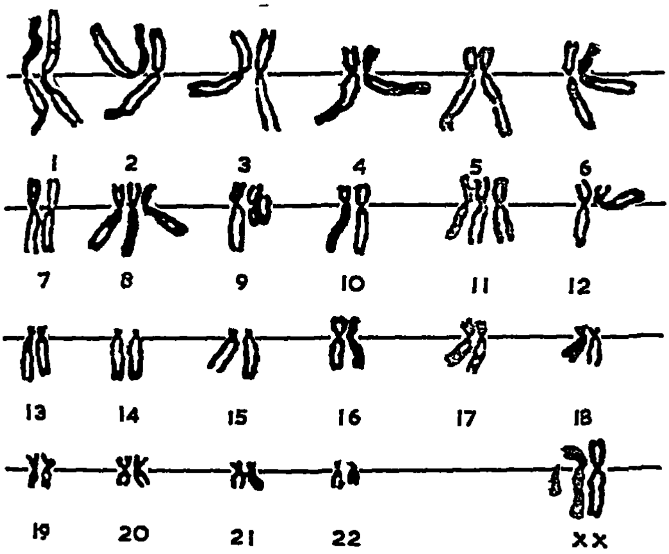

Fig 5—Karyotype of the patient. 49 chromosomes (arranged from a mitotic bone-marrow cell)

Discussion

The uniformity and constancy of the abnormal karyotype, from several independent primary cultures through serial transfers, indicate that the chromosome abnormalities are characteristic of the person Meiotic non-disjunction during gametogenesis of either parent or mitotic non-disjunction at the very early stage of the patient's morphogenesis are the most likely explanations of the origin of the abnormal karyotype The normal karyotypes of the parents and brother, and the lack of evidence for a mosaic of two cell types, are in favour of the first hypothesis There are, however, doubts about the correct interpretation of the karyotype The two trisomics are in the group 6–12, the chromosomes of which are difficult to identify Moreover, we found it difficult to ascertain whether, among the 5 small acrocentrics, there was a Y chromosome or whether the autosome no 21 was present in triplicate

Though cytological evidence seems to favour the first hypothesis, the analysis of the phenotype cannot be considered conclusive

The patient cannot be diagnosed as a case of mongolism or of Klinefelter's syndrome even if he has symptoms which are found in both these syndromes The appearance of the external genitalia and the presence of testicular tissue do not necessarily require the presence of the Y chromosome since we know of similar features in those whose sex chromosomes are of the XX type (*Lancet* 1960b)

In the cases of trisomy for chromosome no 21, and sex chromosomes of the XXY type, there is no evidence of phenotypical overlapping since the affected persons display the classical symptoms of both the mongolian and Klinefelter's syndromes In the present case, even if we do not know what would be the phenotypes of trisomy for chromosome no 8 or no 11, there seems to be a more generalised phenotypical expression of the unbalanced genotype If the sex chromosomes in A B are of the XXY type one would then be tempted to assume that unbalance of one or both autosomes present in triplicate has influenced sex-differentiation Ferguson-Smith et al (1960) recently found that people with sex chromosomes of the XXXY type have the same degree of impairment of sex differentiation as XXY persons, while in A B the [illegible] impairment is more serious It would, however, be too extreme to postulate, on the basis of a single observation, that the autosomes no 8, or no 11, or both, are involved in sexual development, even if the importance for sex-determination of autosome/sex-chromosome balance has been established in lower organisms and cannot yet be rigorously excluded in man

The present case also gives some hints for the general interpretation of chromosomal anomalies It has often been postulated, at least in the case of autosomal trisomy, that a proportionality exists between length of the chromosomes involved and severity of phenotypical expression (among others, Jacobs et al 1960, Edwards et al 1960, Patau et al 1960), with apparent exceptions (De Carli et al 1960, Fraccaro et al 1960b) Evidence from the present case does not seem to favour this postulate

One should, however, make a clear distinction between the clinical and the genetical concept of severity Surprising as it may be that anyone with an anomaly involving two large autosomes can live, it must be remembered that (because of the condition of his reproductive organs) he will not contribute to the next generation and is therefore genetically dead

It is now becoming evident that multiple chromosomal abnormalities are not very rare The origins are as yet obscure Non-disjunction for more than one chromosome at the same meiotic or mitotic event is certainly a possible explanation

To establish firmly the mechanisms underlying these abnormalities, it is of the utmost importance to know the frequencies of each type of aneuploid within populations If multiple abnormalities occur with more than the expected frequency, then other environmental or genetic events leading to aneupoloidy must be sought

The possible existence (in man) of genes tending to produce non-disjunction or asynapsis should be seriously considered (Harnden et al 1960) The study of chromosome aberrations in families, as recently described by Fraccaro et al (1960b) and by Book and Santesson (1960), should prove particularly informative

Summary

A 7-year-old boy had peculiar facies, protruding abdomen, divided scrotum with a penis, and evidence of congenital heart-disease and kidney malformation He appears to be mentally retarded In the right groin there is a testis, devoid of normal structure, with an epididymis

Bone-marrow and skin-cells cultured in vitro displayed a complement of 49 chromosomes, with apparent trisomy for chromosome no 8 and no 11 and the sex chromosomes are of the XXY type Cultured somatic cells from the parents and a brother of the individual had a normal karyotype

This research has been aided in part by a grant from the Swedish Cancer Society to one of us (M F)

During the time of the final preparation of the manuscript one of us (M F) was a guest of the Istituto di Genetica, Università di Pavia

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Addendum

Dr Sylvia Lawler has provided details of blood-group studies made at the Galton laboratory on A B and his parents There was nothing to suggest that the extra chromosomes in the patient carried genes involved in the determination of the blood-group phenotypes The phenotypes are

—	Red cells					
	ABO	MNSs	Rh	P	Lewis	Kell
Father	O	MNss	R_1R_1	P_1	Le(a−b+)	K+k−
Mother	A_1	MSs	rr	P_2	Le(a−b+)	K−k+
A B	A_2	MNss	R_1r	P_1	Le(a+b−)	K−k+
	Lutheran		Duffy		Kidd	
Father	Lu(a−b+)		Fy(a+b+)		Jk(a−b+)	
Mother	Lu(a−b+)		Fy(a−b+)		Jk(a+b+)	
A B	Lu(a−b+)		Fy(a−b+)		Jk(a−b+)	

—	Serum		Secretions
	Haptoglobins	Gm	ABH
Father	1−1	(a−b+x−)	+
Mother	2−1	(a+b+x+)	+
A B	1−1	(a+b+x+)	−

LEIOMYOSARCOMA OF THE LUNG

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Primary smooth-muscle tumours of the lung are rare, but their recognition and treatment are important This is particularly true of the malignant variety which tends to metastasise late

The literature of pulmonary leiomyosarcoma has been reviewed by Hochberg and Crastnopol (1956), Tocker et al (1957), Agnos and Starkey (1958), and Hewlett and McCarty (1958) who collected seventeen cases to which they added one of their own They did not include the two cases of Agnos and Starkey (1958), two reported by Brass (1941), and one by Hicks (1957) Additional cases have since been recorded by Hueck and Matzander (1958), Yacoubian et al (1958), Ochsner and Ochsner (1958), and Glennie et al (1959), making a total of twenty-eight The further case presented here suggests that an early diagnosis might have resulted in successful surgical treatment

Case-record

A man, aged 37, was seen in Aug , 1959 For 2 months he had noticed dyspnœa on exertion and a cough productive of small amounts of mucoid sputum On the day before admission he had a slight hæmoptysis, and later in the day his sputum had been streaked with blood several times He had been a heavy smoker for many years and consumed about 25 cigarettes daily In the past his health had been good, and, as secretary of his local football club, he had been accustomed to physical exertion Routine mass-radiographs in Jan , 1957, and Oct., 1957 (figs 1 and 2), had been reported as normal

Physical examination revealed a robust, sallow man weighing 125 lb There was no dyspnœa or cyanosis at rest, and the pulse was regular with a rate of 120 per minute The blood-pressure was 150/90 mm Hg There was no clubbing of the fingers The chest movements were reduced on the left side, posteriorly and laterally the percussion note, vocal fremitus, and air entry were impaired in the lower zones, and there were no adventitious sounds The heart appeared to be enlarged and the increased pulsation in the epigastrium suggested that this was the result of right ventricular hypertrophy The first and second heart sounds were normal in all areas and a mid-diastolic third sound was audible at the cardiac apex A soft systolic murmur, loudest in mid-systole, was heard over the precordium The jugular venous pressure was normal

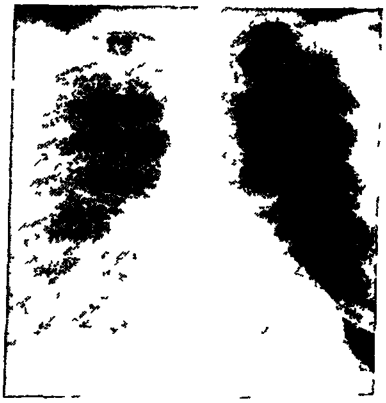
Fig 1—Radiograph of the chest (January, 1957), showing no evidence of the tumour

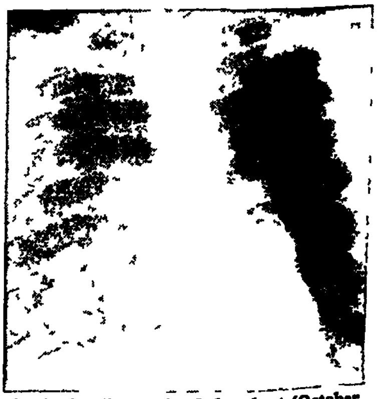
Fig 2—Radiograph of the chest (October, 1957), showing an opacity overlying the left heart border

Investigations

Hæmoglobin 12 7 g per 100 ml , leucocytes 11,000 per c mm (neutrophils 77%), lymphocytes 18%, monocytes 5%) Erythrocyte-sedimentation rate 10 mm in the first hour (Westergren)

Sputum —Mucoid and blood-stained, but no malignant cells could be identified

Electrocardiogram (E C G) —Sinus tachycardia, P pulmonale, T wave inversion in leads I, AVR, AVL, V_3, V_5, and V_7

X-ray of chest (fig 3) —There was a large round soft-tissue shadow at the left hilum, the left main bronchus was displaced upward, and appeared narrow, and the lower-lobe bronchus could not be distinguished The lower half of the chest was opaque The heart appeared enlarged towards the right, but the left border was not visible An examination of the earlier films showed a well-defined opacity overlying the left border of the heart in Oct , 1957 On fluoroscopy of the heart, the opacity appeared to be in contact with the arch of the aorta

Progress

No fluid could be obtained by pleural aspiration 4 days after admission, the patient expectorated 5 oz of fresh blood, and on the following day had a hæmoptysis of over 10 oz This was accompanied by severe shock He was placed on his left side, and given morphine and oxygen, after this treatment his condition improved

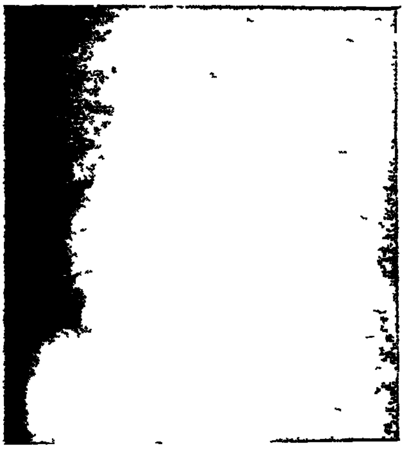

Fig. 3—Radiograph of the chest taken on Aug. 15, 1959 (eight days before death), showing a large rounded shadow at the left hilum, an opaque left lower hemithorax, and displacement of the heart to the right.

The enlarged cardiac shadow was thought to be the result of a pericardial effusion, and on aspiration of the pericardium under E.C.G. control 100 ml. of heavily blood-stained material was withdrawn. The needle was inserted at a point one inch inside the cardiac apex; no resistance was encountered and no myocardial injury pattern was recorded on the E.C.G. A tentative diagnosis of a dissecting aneurysm of the aorta rupturing into the pericardium and bronchus was made, and an operation was considered. However, 24 hours later the patient had another severe hæmoptysis and died within a few minutes.

Necropsy

A whitish tumour (fig. 4) measuring about 13×12×11 cm. was found in the lower lobe of the left lung, the whole lung weighing 2005 g. The left pleural cavity was almost obliterated by dense adhesions, and there was direct neoplastic infiltration of the pleura, diaphragm, mediastinum, and both layers of the pericardium. Sections of the tumour showed extensive areas of hæmorrhage and necrosis, as well as partial encapsulation with compression of surrounding lung-tissue. Whether the neoplasm originated in a bronchus or in some other structure could not be determined. No evidence of metastasis was found in the mediastinal lymph-nodes or elsewhere in the body. Both lungs were congested and œdematous but the heart appeared normal apart from neoplastic infiltration of the epicardium. The cause of death was probably shock following the severe terminal hæmoptysis.

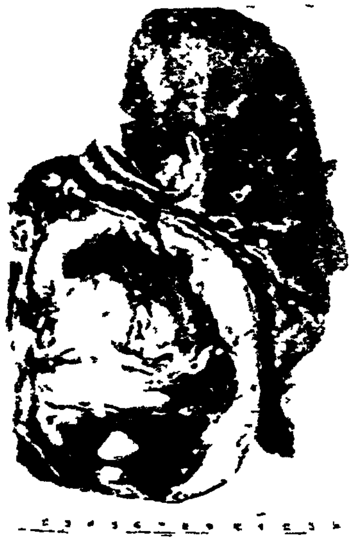

Fig. 4—Cut surface of the left lung showing the hæmorrhagic tumour in the lower lobe.

Histological Examination

Sections showed a tumour with a variable structural pattern. In some parts there were interlacing bundles of spindle-shaped cells with elongated, blunt-ended nuclei and eosinophilic cytoplasm closely resembling smooth muscle (fig. 5). The cytoplasm stained yellow by Van Gieson's method and the reticulin-pattern was sarcomatous rather than carcinomatous. Staining by the picro-Mallory method and by phosphotungstic-acid-hæmatoxylin suggested a smooth-muscle origin. In other parts the tumour was poorly differentiated, the cells being oval or rounded, with little cytoplasm and numerous mitoses (fig. 6). The growth was fairly vascular and there was evidence of neoplastic infiltration of thin-walled blood vessels with thrombosis and areas of hæmorrhage and necrosis. Between the cells there was a variable amount of collagen, which in some areas was dense and hyaline, and associated with degenerative changes in the tumour. The structure was that of a leiomyosarcoma.

Discussion

This patient presented a difficult diagnostic problem, particularly as it was assumed that the previous radiographs were normal. At the time that the patient was seen, the radiological appearances (fig. 3) differed from those described by Sherman and Malone (1950) as characteristic of leiomyosarcoma, and the abnormal cardiac signs drew unwarranted attention to the cardiovascular system. On fluoroscopy of the heart, the opacity was seen to be in contact with the arch of the aorta, and needle-aspiration of the pericardium produced heavily blood-stained fluid. A dissecting aneurysm of the aorta seemed the most probable diagnosis. Necropsy, however, demonstrated that there was no blood in the pericardial sac and that the aspirated fluid had come from a necrotic area of the tumour.

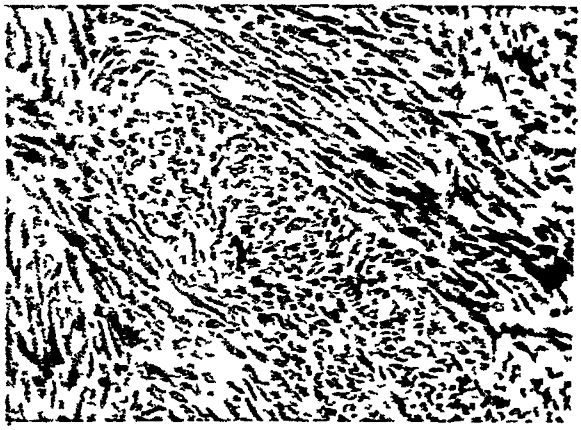

Fig. 5—Spindle-shaped cells arranged in bundles resembling smooth muscle, from a more differentiated part of the tumour. (Hæmatoxylin and eosin. ×220.)

An interesting feature of this case was the interval of nearly 2 years between the time when the tumour became apparent and the attendance of the patient. Of the other

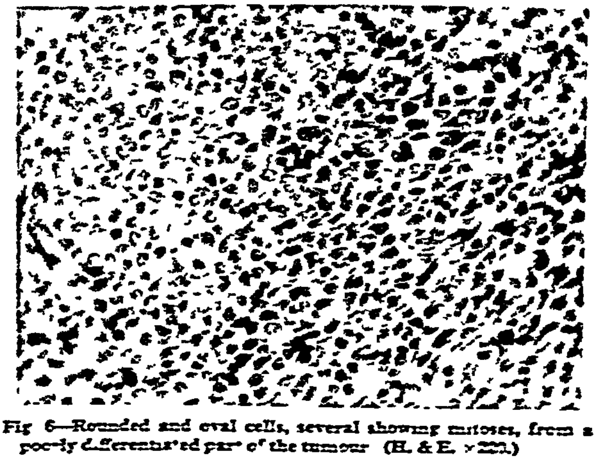

Fig. 6—Rounded and oval cells, several showing mitoses, from a poorly differentiated part of the tumour. (H. & E. ×220.)

twenty-eight cases found in the literature, seven had clinical histories of 2 years or more, the one reported by Brunn and Goldman (1940) being remarkable in that the patient had had an increasingly productive cough for 10 years before removal of the tumour

The age-incidence of the reported cases covered a wide range of from 4 to 83 years with an average of 43 6 years The sexes were equally affected The commonest site was in the left lower lobe where there were six examples (the present case making the seventh) The right lower lobe was involved in five cases, the right upper lobe in four, the right middle lobe in three, and the left upper lobe in two Other sites were—the main bronchi (three), the trachea (one), and the left visceral pleura (one), in three cases the site was not clearly stated The precise structure from which each tumour arose was not always easy to determine (as in the present case) and was often a matter of conjecture, but a bronchus was thought to be the origin in thirteen cases The tumour size was variable, but was often large—being 10 cm or more in diameter in nine cases, those reported by Catron (1931) (22×8×18 cm), and by Mishkin (1951) (20 cm diameter) being outstanding Hæmorrhage was often present There were nine instances of neoplastic infiltration of adjacent tissues The pleura was most often involved, followed by the pericardium and chest wall, then the diaphragm, pulmonary veins, and regional lymph-nodes, and lastly the mediastinum Metastasis took place in only five cases, although death occurred in three others without any necropsy being made Surgical resection was carried out in eighteen cases, in thirteen of which there was no recurrence of the tumour

Pulmonary leiomyosarcoma differs widely in clinical aspects, growth, and spread from bronchogenic carcinoma, and has a more favourable prognosis

Summary

A case of pulmonary leiomyosarcoma is described and the literature is briefly reviewed, twenty-eight previously reported cases having been found These tumours tend to metastasise late, so that the clinical history may often be comparatively long Early radiological recognition is clearly important and might have altered the outcome in the present case, which became a difficult diagnostic problem because of cardiac involvement

We wish to thank Dr N C Oswald for his helpful criticism, Mr J W Miller for histological sections, Mr N K Harrison for the photographs, and Mr P R Crocker for the photomicrographs

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" Medicine has always demanded and has always received the upper level of mental ability among those graduating from the colleges of the nation However, medicine is facing increasing competition for these same college students As the world progresses further into the age of technology, this competition will become more serious Engineers, scientists, and educators are looking to these same superior college students for their future leaders "—J Z APPEL, *J Amer med Ass* 1960, 173, 1446

RENAL CARBUNCLE WITH PERFORATION INTO THE PERITONEAL CAVITY

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LOCALISED suppuration in one segment of a kidne leading to abscess formation, is not often seen, despite t large number of cases (over two hundred) in the literatu The infection reaches the kidney through the blood-strea and the organism responsible is almost always *Staph lococcus aureus*. The recognised complications of ren carbuncle include perinephric suppuration and pyæm followed by pyuria Perforation into the peritoneal cav has not previously been reported A case of bilater pyonephrosis with subsequent unilateral perforation in the peritoneum (Gorog 1948) bears some resemblance

Case-report

A 58-year-old fettler was seen in the outpatient departme on the morning of Feb 13, 1960, complaining of varicose vein During examination he volunteered that he had been sufferin from intermittent mild abdominal pain and anorexia for th previous four to six weeks The pain was in the epigastriu and right hypochondrium, and had no association with meal Nothing abnormal was found on examination of his abdomen

At 11 A M the next day he was admitted as an emergency complaining of severe generalised abdominal pain, which starte the previous afternoon and developed to its full intensity i one and a half hours. The pain was continuous, maximal o the right side, and made worse by movement He had vomite four times before admission He had had dysuria and frequenc with cloudy urine eight weeks before which had lasted on week

He appeared pale and obviously ill Temperature was 100°F (37 8°C), pulse-rate 112 per minute, and blood-pressure 170/120 mm Hg His tongue was dry and coated The abdomen was found to be rigid and very tender, particularly on the right side No bowel sounds were heard A white-cell count showed a neutrophil leucocytosis with a total count of 24,000 per c mm

A diagnosis of general peritonitis, probably the result of a perforated appendix, was made

The abdomen was opened through a right paramedian incision and thick creamy pus was found in the peritoneal cavity The appendix was normal, there was no Meckel's diverticulum, and the stomach and duodenum showed no abnormality Thick purulent fluid was found in large quantities in all parts of the abdomen and pelvis The hepatic flexure of the colon was adherent to the lower pole of the right kidney, and on examining this area a small hole about one centimetre (3/8 in) in diameter was seen on the anterior surface of the kidney lateral to the flexure Pus was exuding from this hole and pressure on adjacent renal tissue increased the flow. Further exploration revealed an abscess occupying the lower pole of the kidney, the perinephric space appearing unaffected Transabdominal nephrectomy was performed The abdomen was closed leaving a stab-drain leading to the renal bed After the operation the patient received systemic penicillin and streptomycin

The kidney contained one large and several small abscesses, all in the lower pole, the rest being normal The peritoneum was adherent over the region of the large abscess, with obvious perforation into the peritoneal cavity Culture of the pus grew penicillin-sensitive *Staphylococcus aureus*

After a good initial recovery retention of urine developed because of prostatic hypertrophy, which, after catheter drainage, was treated by retropubic prostatectomy on March 7, 1960 After this setback, recovery was uneventful.

Discussion

Renal carbuncle is usually secondary to infected cutaneous lesions (Rose 1953) This patient could not remember having suffered from any such lesion in the past few years An insignificant scratch or some oropharyngeal lesion (Cabot 1936) may, however, have been the primary source

The vagueness of the symptoms and lack of localised tenderness the previous day is surprising The relevance of the urinary symptoms eight weeks previously is doubtful This was probably an episode of urinary infection, but it could hardly have been the cause of such a purely parenchymatous lesion as a carbuncle

Recent authors advise conservative management in this condition—by incision and drainage (Shearer et al 1945, Rose 1953), with the administration of antibiotics locally (Rosina and Galdini 1953), and systemically (Stadeven 1955, McAllister and O'Connor 1945) Welch and Prather (1949) aborted a case by antibiotics alone. In this case the only possible treatment was nephrectomy because of the communication with the peritoneal cavity.

Summary

A case of peritonitis caused by a renal carbuncle perforating into the peritoneal cavity is presented and discussed.

Treatment by nephrectomy and systemic antibiotics resulted in recovery, intercurrent retention of urine necessitated prostatectomy in the postoperative period.

I wish to thank Mr Derek Lambley for permission to publish this case.

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Preliminary Communication

TREATMENT OF CARBON-MONOXIDE POISONING WITH OXYGEN UNDER PRESSURE

ANOXIA is generally believed to be the main factor causing death in cases of domestic-gas poisoning, partly because of the blocking of hæmoglobin for oxygen transport by the more stable carboxyhæmoglobin, and more particularly because of the " shift to the left " which this compound causes in the dissociation curve of oxyhæmoglobin. The toxic effect of carbon-monoxide gas itself is usually considered unimportant, although Halperin et al.[1] adduce persuasive evidence of possible effects of the gas besides anoxia. In this department we have shown that in experimental acute carbon-monoxide poisoning in animals the anoxia can be rapidly corrected by pressurisation to 2 atmospheres of oxygen[2] By this means the cellular anoxia is immediately corrected, and furthermore it follows from the Law of Mass Action that the equilibrium of the equation $Hb + CO \rightleftharpoons HbCO$ will be shifted to the left and more hæmoglobin which can combine with oxygen will be liberated. The carbon monoxide is excreted through the lungs and normal oxygen transport by the blood is restored. This being so, there were clear indications for applying this principle to cases of carbon-monoxide poisoning in man.

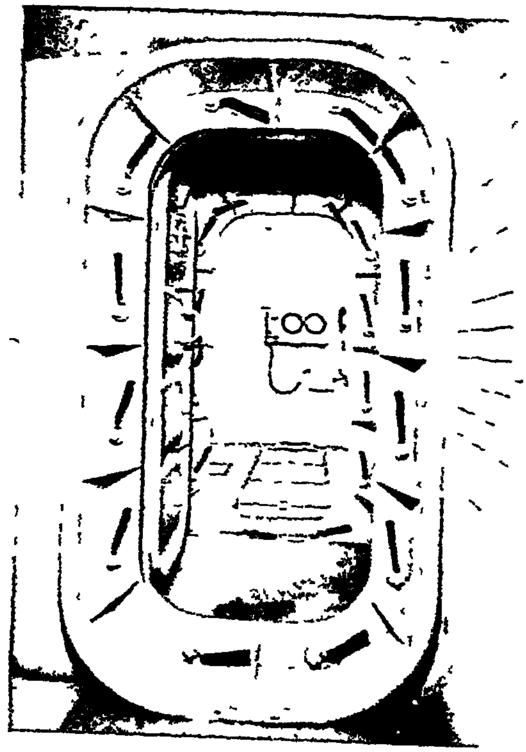
A large pressure vessel was built in this department to design prepared in cooperation with emeritus Prof. Andrew M. Robb (naval architecture) This pressure chamber (see accompanying figure) can accommodate both patients and medical staff. On Sept. 19, 1960, two patients gassed with household gas were successfully treated in the chamber

Case 1.—A 19-year-old woman was found unconscious in a gas-filled room by an ambulance team and was brought to hospital. Oxygen and artificial respiration were provided by Stephenson's cycling resuscitator On arrival the patient was breathing spontaneously and all reflexes were present, but she could be roused only with difficulty She was placed in the chamber, breathing oxygen, while the pressure was raised to lb per sq in.

Case 2.—A man, aged 47, who had been found in a gas-filled room and who was deeply unconscious, was brought to hospital on Stephenson's resuscitator at this time. On admission he was in deep coma, ashen-grey, with widely dilated pupils and spasticity of the upper limbs Spontaneous respiration was absent and no pulse could be detected. The pressure in the chamber was lowered in order to admit this man.

Blood samples were then taken from both patients, and the chamber pressure was raised to 15 lb per sq in. over 15 minutes, during which time both patients were given oxygen.

After about 10 minutes in this environment, electroencephalograph (E.E.G.) and electrocardiograph (E.C.G.) leads were attached to case 2 By now case 1 appeared to have revived, she could talk intelligently and was able to hold the oxygen-giving set herself In case 2 the spasticity of the limbs disappeared, the pupils again reacted briskly to light, the colour reverted to normal, and after about 20 minutes he began to breathe without the aid of the resuscitator Soon after he opened his eyes when spoken



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CARBOXYHÆMOGLOBIN LEVELS IN VENOUS BLOOD

Case no	Before pressurising	After pressurising
1	26%	0%
2	50%	0%

to, and after 40 minutes he answered questions and moved his limbs purposefully Parallel changes were shown by the EEG tracings The ECG appearance improved strikingly from a very-low-voltage pattern with cardiac irregularities and a rate of 180 per min to a normal voltage and a sinus tachycardia of 120 per min At the end of an hour, as both patients were fully conscious and their colour was good, the chamber pressure was reduced to normal atmospheric pressure over a period of 30 minutes Both patients were returned to bed after a sample of venous blood had been taken from each

Both patients had their chests X-rayed and blood biochemistry investigated next day when recovery appeared complete The results of these investigations were within normal limits

Before compression to 2 atmospheres of oxygen, case 1 had a venous blood carboxyhæmoglobin content of 26% (the pressure was then reduced after the patient had already been in high-pressure oxygen so as to admit the second case) Before pressurisation, case 2 had a carboxyhæmoglobin content of 50% At the end of the period of pressurisation blood from both patients contained no carboxyhæmoglobin These estimations were performed by Hartridge's quantitative methods, using a reversion spectroscope [3]

DISCUSSION

Case 1 might have responded to conventional treatment, but case 2 would normally have been classified a moribund Hence we believe that our technique was life saving Each additional minute of anoxia and of carbon monoxide intoxication diminishes the likelihood of th patient's recovery The body must be rid of carbo monoxide by the most rapid and effective metho compatible with the safety of both the attendant an patient We believe that our method fulfils thes requirements

Our thanks are due to Prof C F W Illingworth who instigate and encouraged research in this field, to Prof A W Robb, and to th industrial firms who cooperated in the construction of the pressur chamber, funds for which were made available by the Department o Health for Scotland on the recommendation of the Advisory Committee for Medical Research

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Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS AND ASSOCIATION OF CLINICAL BIOCHEMISTS

THE 65th general meeting of the Association of Clinical Pathologists was held in London on Sept 29 to Oct 1 The last day was a joint meeting with the Association of Clinical Biochemists The following are summaries of some of the contributions to the pathologists' meeting

Hospital Cross-infection

Dr L STEINGOLD and Dr L VOGEL remarked that finding causes of hospital cross-infection, and devising methods of correcting the faults, presented little difficulty the difficulty lay in introducing such methods into the wards and theatres, and, even more, in seeing that they were continued indefinitely once they had been introduced—over a whole hospital, this seemed impossible, apparently because of poor staff morale Staff were enthusiastic at first but sooner or later lost interest and reverted to their previous unsatisfactory techniques A possible explanation lay in the conditions under which staff worked in most hospitals Advances in clinical techniques had not been accompanied by the necessary improvements in design, staffing, and equipment of hospitals The more obvious parts of a hospital were usually reasonably adequate Thus, operations were generally performed in a reasonably adequate operating space, and patients were usually accommodated in reasonably adequate wards The accommodation for other work, however, was often grossly inadequate Thus, bathrooms, sluice-rooms, dressing-rooms, changing-rooms, and storage facilities might be poor or absent, and cleaning and sterilisation equipment may be out-of-date or makeshift

Virus Infections of the Central Nervous System

Discussing the investigation of these infections, Dr F O MACCALLUM said that as no specific treatment for virus infections was yet available, tests which would identify possible bacterial pathogens obviously took priority, as did CSF examination If no organism was identified within twenty-four hours then specimens for virus isolation and information on amounts of protein and cells in the CSF, white blood-count, temperature pattern, and a few pertinent points of clinical history should be provided to the laboratory If the illness began more than three weeks before admission, virus investigations were unlikely to be of value (for specimens required and methods of investigation see *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service*, 1957, 16, 151) Virus may be found in throat, stools, and cerebrospinal fluid Stools were the best source of virus in infections with polio (3 types), Coxsackie (25–30 types), and Echo viruses (more than 28 viruses) Throat swabs and particularly CSF, when available, were necessary for mumps, lymphocytic choriomeningitis, louping ill, and herpes infections Serum in the acute stage and fourteen to twenty-one days from onset should be provided to verify the significance of the virus isolated, or for selected tests when no virus was isolated

Atypical Acid-fast Bacilli

Dr A BECK reported that four cultures of photochromogenic mycobacteria which had been isolated repeatedly from patients with a disease resembling tuberculosis were compared serologically with the human tubercle bacillus strain H37Rv and with *Mycobacterium phlei* and *Myco smegmatis* Antise against these cultures were examined by the Middlebro test using PPD fractions of mycobacteria as antigens for re cell sensitisation Titration of these sera revealed considerab cross-reactivity By the use of absorption and inhibitic techniques, however, a specific antigen could be demonstrat in photochromogens In addition to this they were found have a common antigen with the human tubercle bacillus stra H37Rv, and a third antigen which was shared by all the myc bacterial species examined These results support the view th atypical acid-fast bacilli represent a special group of myc bacteria distinct from both tubercle bacilli and saprophyt mycobacteria

Indigenous Amœbiasis

Air Commodore W P STAMM drew attention to the chron insidious symptoms in most cases of intestinal amœbiasis an to the further difficulty in diagnosis caused by a 5–10 incidence of carriers of *Entamœba histolytica* in the Unite Kingdom He thought that civilian routine laboratories d not report such a high incidence because direct microscopy of fæces was not practised as a routine and, pathologists and technicians were often inexperienced in fæcal protozoology He warned against operating on a patient who had been overseas and presented with an abdominal tumour, without first examining the stools carefully

Malaria in the United Kingdom

Wing-Commander R. Mortimer said that the most important tropical disease likely to be encountered in the United Kingdom was malignant tertian malaria, which in its pernicious forms, particularly cerebral malaria, was still killing people. The possibility of malaria should always be considered in any patient with a fever who arrived in this country from the Tropics via central Africa about ten to fourteen days previously with perhaps a history of an unscheduled night stop en route. There was usually no difficulty in demonstrating parasites in blood-films and, if found, the results should be phoned at once to the ward so that treatment can begin with the minimum delay All patients with pernicious malignant tertian malaria should be treated as emergencies with intravenous or intramuscular chloroquine or intravenous quinine Delay in treatment or treatment by mouth might result in tragedy

Punch Actinomycosis

Dr H I Winner described how a man damaged the back of his right index finger hitting someone in the teeth. He was treated with penicillin for four days Although the skin injury healed, the finger became swollen and painful, and remained so for three months At the end of this time it became acutely inflamed X-ray examination now showed rarefaction of the head of the proximal phalanx Open operation revealed much pus in the subcutaneous tissues, containing numerous "sulphur granules" in which *Actinomyces israeli* was identified After operation he was treated with penicillin and streptomycin for a week, and thereafter with penicillin for four months Uneventful cure followed. Four similar cases have been found in the literature.

* * *

The proceedings of the joint meeting included the following

Malabsorption Syndrome

Prof A. C. Frazer said that the primary ætiological factor in the malabsorption syndrome may be faulty intraluminar preparation for absorption, due to lack of pancreatic enzymes or bile salts, or incoordination of gastrointestinal function A secondary enteropathy may be superimposed by electrolyte imbalance or bacterial infestation A primary enteropathy may arise from gluten intolerance, folic-acid deficiency, bacterial infestation or small intestinal disease, or a combination of two or more of these factors A deleterious agent could be demonstrated in wheat gluten which inhibits small intestinal motility by interference with acetylcholine release. This substance was ultrafiltrable, heat-stable, and resistant to peptic/tryptic digestion, but its action was destroyed by incubation with extract of small intestinal mucous membrane Gluten or appropriate fractions cause deterioration in patients in remission on a gluten-free regimen Gluten intolerance may be a major or a secondary ætiological factor Bacterial infestation of the small intestinal lumen may be a major factor, as in gastrocolic fistula and loop syndromes, it may also play an important part in other forms of the malabsorption syndrome Small intestinal disease, such as regional enteritis, lymphatic obstruction, or Whipple's disease, may be associated with the malabsorption syndrome Whatever the cause, unabsorbed food materials passed into the lower reaches of the bowel and gave rise to increased bacterial activity The flora modified many of the fæcal constituents In some cases significant amounts of fat and nitrogen that were not of direct dietary origin may be found in the stools

^{131}I-labelled Fat in Diagnosis of Steatorrhœa

Dr M. Lubran described how absorption of fat from the intestine could be investigated satisfactorily by measuring the fæcal radioactivity for four days after an oral dose of 10 μC of ^{131}I-triolein Of 183 tests carried out simultaneously with a six-day chemical fat determination, complete agreement between the two tests was found in 139 (76%) of tests and borderline agreement in a further 44 (13 7%) The radioactive and six-day chemical fat tests were about equally effective in detecting steatorrhœa Because of the fluctuations in the fæcal excretion of fat in steatorrhœa, however, it may be necessary to carry out daily measurements of fæcal fat for a long time Radioactive fats are not suitable for long-continued measurements

Lipæmia, Coagulation, and Thrombolysis in Ischæmic Heart-disease

Dr D C O James, Miss J Drysdale, Dr J D Billimoria and Prof N F Maclagan had compared lipæmia, coagulation and thrombolysis in 28 normal subjects, 24 patients with angina pectoris, and 34 with myocardial infarction All subjects were between 40 and 70 The normals had no evidence of ischæmic heart-disease, hypertension, nephritis, diabetes mellitus, xanthomatosis or thyroid disease and, all had a normal E C G The tests were carried out under standard conditions, with and without inclusion of butter in the test breakfast Under fat-free conditions the lipæmia in normal males under 40 was significantly higher than in normal females under 40 Significant differences from normal were noted in the pathological groups thus, the angina group showed a higher lipæmia, a shorter stypven time, and a longer thrombolysis time, while the infarction group showed similar trends but the differences from normal were less significant The differences due to inclusion of $1^1/_2$ oz. of butter in the test breakfast were not sufficiently significant to justify the use of fat-feeding tests in the investigation of ischæmic heart-disease Anticoagulants (phenylindanedione) decreased the lysis time. The interval between myocardial infarction and the tests did not seem to influence the results The findings as a whole indicated some disturbance of plasma-lipids and of coagulation and thrombolytic mechanisms in ischæmia heart-disease which were much more significant in angina pectoris than in myocardial infarction

17-Hydroxycorticosteroid Excretion in Peptic Ulcer

Mr A G Green and Dr C N Pulvertaft found that the mean excretion of 17-hydroxycorticosteroids in 90 men with active duodenal ulcers was 8 8 mg per day, significantly lower than that in 52 normal men (11 6 mg per day) (the age-distribution for these groups was very similar) 28 men with active gastric ulcers had a mean output of 7 8 mg per day, 40 men who had undergone partial gastrectomy for duodenal ulcer some ten to fifteen years previously showed a mean output of 7 8 mg per day, the mean for 29 men with duodenal ulcers in a quiescent phase was also 7 8 mg per day For these three groups the mean age was slightly higher than that of the controls and the active-duodenal-ulcer group Very little difference was found in the excretion of 17-ketosteroids between the control and duodenal-ulcer groups The excretion of 17-ketosteroids in the gastric ulcer and post-gastrectomy groups was slightly lower than in the control group

In the active-ulcer group a definite correlation was noted between 17-H C S excretion and the volume of urine (D U, $r = 0\ 52$, G U, $r = 0\ 49$) A similar correlation was found for the post-gastrectomy group ($r = 0\ 54$) This finding was not observed in the controls ($r = 0\ 11$) and the quiescent-ulcer group ($r = 0\ 23$)

The excretion of 17-H C S was estimated before and six months after partial gastrectomy for peptic ulceration in 18 men In 13 of these the postoperative excretion was less than the preoperative level, the mean falling from 9 9 to 6 9 mg per day A similar observation for 17-ketosteroids excretion was noted in 23 out of 28 cases, the mean falling from 11 4 to 8 3 mg per day This fall was not observed after vagotomy and gastroenterostomy (23 cases) when there was very little difference in the pre- and post-operative levels

Electrolytes in Intestinal Disease

Dr J P Nicholson and Dr J F Zilva had measured total exchangeable sodium and potassium values in 19 patients with intestinal diseases, particularly ulcerative colitis Generally speaking, the exchangeable sodium values were within the normal range while the exchangeable potassium values were well below the normal limits The picture was complicated by the fact that steroids were often used to treat these conditions Further information may be obtained by considering the two values in conjunction—i e, the sum of sodium and potassium, and their ratio

New Inventions

A BRONCHIAL FLOW METER

THE traditional method of measuring the function of part of the lungs is bronchospirometry This technique has several disadvantages, however, the chief of which are that the passage of a large catheter is unpleasant for the patient, the conditions are unphysiological, and in general only the comparison of one lung with the other is practicable Recently, regional lung function has been measured successfully by sampling in lobar and segmental bronchi at the end of routine diagnostic bronchoscopy, using a special mass spectrometer as a continuous rapid gas analyser [1] This procedure is much more informative than bronchospirometry, and has the advantages of interfering less with normal physiological conditions, and of not subjecting the patient to an additional investigation

Unfortunately a mass spectrometer is a formidable instrument, only likely to be found in specialised laboratories But the bronchial flow meter described here may be used with other less expensive gas analysers which are within the reach of large general hospitals By using the flow meter, measurements of air-flow in various segmental bronchi can be made at bronchoscopy in a few minutes, giving an excellent guide to the relative function of different parts of the lung

Principle

The flow meter consists of two long fine tubes with right-angled ends These are opposed, with a small separating gap (fig 1) A tracer gas, for example helium, is blown down one tube, and the other tube is connected to a vacuum pump and gas analyser The helium streaming across the gap is deflected by the bronchial gas-flow at right angles to it, and the helium signal from the gas analyser is thus a measure of bronchial flow

Construction

The tubes are of stainless steel hypodermic tubing, about 120 cm long and of 0 3 mm bore The 0 5 mm gap between the ends of the tubes is protected by a fine stainless-steel wire cage of 6 mm outside diameter The tube to the gas analyser is warmed by an electric current to prevent water-vapour condensation

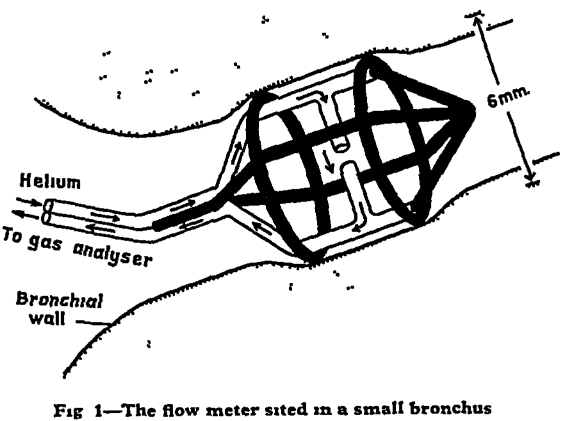

Fig 1—The flow meter sited in a small bronchus

The tracer gas (helium) is blown across the 0 5 mm gap, and any bronchial gas-flow deflects this jet so that the gas analyser records a reduced concentration

Technique

The tracer gas is delivered from a pressure cylinder via a commercial pressure-reducing valve, and in the case of helium, a rapidly responding helium katharometer is a convenient analyser Alternatively a fast nitrogen meter would be satisfactory if a nitrogen-free gas, for example oxygen, were used as the tracer, in this case the approximately equal concentrations of nitrogen in inspired and expired air would be exploited. The flow meter can be successfully placed in the majority of segmental bronchi which can be seen by direct vision at bronchoscopy The bronchoscope should then be withdrawn into the trachea to minimise any interference with the natural air-flow The flow meter itself causes negligible obstruction

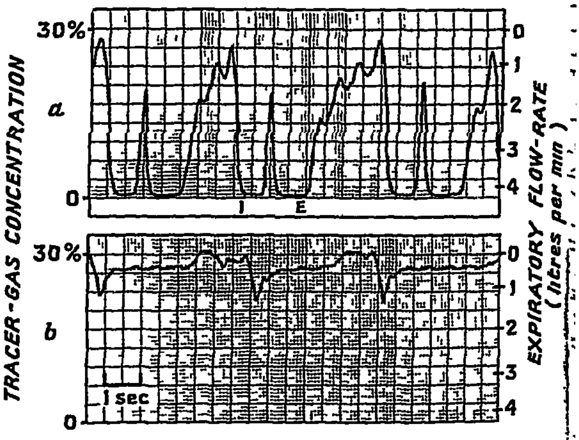

Fig 2—Tracings taken (a) with the flow meter in the normal right lower lobe and (b) in the diseased left-lower lobe of a patient with unilateral emphysema

When there was no bronchial flow the tracer-gas concentration was 30%, both inspiratory and expiratory flow (I and E) reduced this The expiratory flow-rate was higher than 4 litres per min on the normal side, but grossly reduced on the abnormal side The calibration for inspiratory flow was not quite the same as for expiratory flow, and has been omitted for clarity

Calibration

The flow meter measures the flow-velocity of the bronchial gas in the region of the tracer-gas jet In clinical work it often suffices to know whether part of the lung is ventilating or not But the cage has been designed to distend slightly a segmental bronchus, and under these conditions the flow meter can be used to measure volume flow-rate It is calibrated by placing it within a glass tube of 6 mm internal diameter, through which air is blown to a rotameter Various errors related to the velocity profile have been discussed elsewhere [2] Although the flow meter does not give the direction of flow this normally causes no confusion When studying the mechanical properties of the lung the instants at which bronchial-flow reverses are of interest are displayed very clearly (fig 2) The response-time of the measurements will be limited by that of the gas analyser

The flow meter has been patented through the National Research Development Corporation, and it is manufactured by Godart-Mijnhardt, Ltd, 97, Maidstone Road, Rochester, Kent

I should like to thank Dr Philip Hugh-Jones and Mr L Smith for valuable help The work was supported by the Medical Research Council

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[1] Hugh-Jones, P, West, J B *Thorax*, 1960, 15, 154

[2] West, J B *J appl Physiol* 1960, 15, 976

Reviews of Books

Nitrous Oxide in Dentistry

Its Danger and Alternatives J G BOURNE, M.D., F.F.A. R.C.S., senior consultant anæsthetist, St. Thomas's Hospital, London. London: Lloyd-Luke (Medical Books). 1960. Pp. 181. 30s.

Dr Bourne estimates that about 2½ million administrations of general anæsthesia are given yearly to ambulatory patients in this country, and that in three-quarters of these nitrous oxide is given. Like some of the early users of this type of anæsthesia, he was not happy about a method whose success depended on oxygen deprivation. This book records the conclusions he reached after personal observation and experiment, and after examining the answers to a questionary he sent to a large number of dentists.[1] Nitrous-oxide administration is apparently simple, and it is therefore used by doctors who may have much or very little experience of its use. Even in experienced hands troubles are not rare. Struggling and convulsive movements may occur, anæsthesia may be poor, cyanosis is the rule, respiration may fail, and full recovery may be delayed for hours or even days. Occasionally the outcome is fatal, and sometimes the patient is left with minor or major changes in temperament and intellectual ability. Dr Bourne believes and produces evidence for his belief, that the low anæsthetic potency of nitrous oxide combined with the inevitable hypoxia, often severe, makes its use undesirable. He points out how often it is used when the patient is sitting, and how easy it is to miss the fact that an unconscious patient has fainted and needs to be placed horizontal so that the cerebral anæmia is relieved before permanent damage is done to the central nervous system.

If nitrous oxide is to be banned as ineffective and dangerous, some other and more satisfactory anæsthetic must be found for ambulatory patients. The chosen drug should induce anæsthesia quickly, permit rapid recovery, prevent awareness of pain, be easy to use, and have a wide margin of safety. Dr Bourne tried thiopentone, which has its supporters and its advantages. But recovery is slow, and he concluded that inhalation anæsthesia was better. The ideal substance should have a low blood solubility since this would hasten both onset and recovery from anæsthesia, but its potency should be moderate rather than great, to minimise risk of overdosage. An examination of several anæsthetics suggested that cyclopropane was nearest to the ideal, and a method is described which enables the occasional anæsthetist to use it simply and without risk of overdosage. Explosion hazards are avoided by using 40% cyclopropane with 30% oxygen and 30% nitrogen. This mixture was found to give full anæsthesia for about 1½ minutes from the time of removal of the mask. Failures and complications were few.

At the end of the book a chapter is devoted to a discussion of fainting in dentistry and surgery, and Dr Bourne suggests that it is risky and unnecessary to prop up patients after operation since, like patients unconscious in a dental chair, they may faint, and being unable to fall flat may suffer permanent damage from anoxia of the central nervous system.

Dr Bourne's ideas merit open-minded and serious attention. That nitrous oxide is widely used neither sanctifies it nor makes it good; in fact the case against its use is strong. Whether cyclopropane is the ideal replacement remains to be determined; the pharmaceutical chemists may produce something better. Meanwhile, this book should be read and pondered by all anæsthetists, occasional or whole-time.

The Search for New Antibiotics

G F GAUSE, professor and scientific director, Institute of Antibiotics, Academy of Medical Sciences, Moscow. New Haven: Yale University Press. London: Oxford University Press. 1960. Pp. 97. 38s.

THIS monograph describes lines of work recently pursued in the Moscow Institute of Antibiotics, and also some observations made in London in 1959 during the author's sojourn with J W Lightbown and his colleagues at the National Institute for Medical Research. There are three chapters, dealing with soil microbiology, a classification of antibiotic-producing microorganisms, and anti-cancer agents.

In the exhaustive programme of screening microorganisms from different soils, the investigator must choose his soil samples with discrimination and he must evolve a rapid preliminary diagnostic screen to assess the antibiotic-producing potential of the specimens. The screen must identify cultures producing new antibiotics so that the endless repetition of isolating already known antibiotics is avoided. This differentiation is helped by an early classification of antibiotic-producing microorganisms, and the importance of this classification is made clear in the second chapter. In a final chapter the principles enunciated are applied to a preliminary screening programme for detecting anti-cancer agents using as indicators mutant microorganisms with impaired respiration. Unlike antimicrobial antibiotics, anti-cancer agents preferentially inhibit the growth of these mutants rather than the parent culture. Promising agents uncovered in this way could be selected for further studies on animal tumours.

Although the quest must often involve much dull routine, Dr Gause succeeds in conveying an exciting and highly readable adventure. He gives an authoritative and clear account of the problems involved and provides a source of Russian references which might not otherwise be widely known. But even more important is the way he has projected antibiotics, like a sputnik, from the confines of medicine into the widest spaces of biology, where even more can be expected of them in the years to come.

Fractures, Dislocations, and Sprains

PHILIP WILES, M.S., F.R.C.S., honorary consulting orthopædic surgeon, Middlesex Hospital. London: J. & A. Churchill. 1960. Pp. 67. 27s. 6d.

STUDENTS of the Middlesex Hospital, and those who have visited its orthopædic department in recent years, will recall the striking display of wall charts depicting the diagnostic characteristics and modes of treatment of all the common fractures. These charts, with many new photographs and an augmented text, form the basis of this present book. Two facing pages are devoted to each group of injuries (shoulder dislocations, cervical-spine fractures, &c.); on one of them appears a selection of appropriate radiographs, on the other, a set of line drawings and some brief notes on such points as the circumstances in which the lesions are usually sustained and their complications. The style throughout is, by design, somewhat didactic, and the approach conservative. But it is hard to conceive a simpler, safer, or more helpful manual for the use of junior casualty staff. The publishers are to be congratulated on making available to them at such a low price a book which contains over 500 illustrations.

Medical Physics

Vol. 3. Editor OTTO GLASSER, PH.D., head, department of biophysics, Cleveland Clinic Foundation, Ohio. Chicago: Year Book Publishers. London: Interscience Publishers. 1960. Pp. 754. 188s.

THIS volume, like its predecessors of 1944 and 1950, evokes a sense of wonder at the many applications of physics to medicine. It gives a bird's-eye-view of a subject that extends far beyond radiotherapy and ionising radiations to include, for example, blood-flow determinations, interference microscopy, and the applications of strain gauges. The articles on space medicine and the biological hazards of space radiations will enable parents to make intelligent comment on Dan Dare's latest exploits. Its greatest value, however, will be as a work of reference, to give quickly some insight into a branch of the subject outside the reader's normal orbit.

All except one of the 190 contributors come from the U.S.A. —and the exception is a Canadian. Each chapter gives copious references, but several authors seem to neglect the European work. The allocation of space is intriguing, although the average article is 4 pages long, oximetry fills 30 fascinating pages and psychophysics 6, while only $4^1/_2$ pages goes to medical electronics—a subject which has been far from static in the past ten years Short chapters are the rule, and many of them are necessarily superficial and lack authority Unfortunately, the production is less pleasing than formerly and the lines of text are of irritatingly irregular length

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[1] Bourne, J G *Lancet*, 1957, ii, 499.

Many chapters are non-technical and intended for the clinician who needs a straightforward account of the help physics can give, and this is on occasion an admirable approach, which could perhaps be followed on this side of the Atlantic too Other chapters are very detailed, with full mathematical derivations The book is intended to be used in conjunction with the two earlier volumes, which are constantly referred to While many of the articles in volume 3 are new accounts of the subject, others are written to supplement what is in the earlier volumes, and in others reference is made to articles in the earlier volumes without any addition in this volume

Dr Glasser has again earned our thanks for the production of a very valuable encyclopædia

Introduction to Health Statistics

SATYA SWAROOP, PH D, M P H, F N I, chief statistician, health statistical methodology section, World Health Organisation, Geneva Edinburgh E & S Livingstone 1960 Pp 343 40*s*

THE author uses the rather unfamiliar phrase "health statistics" to denote the problems of collecting and interpreting statistical data which face a statistician in a department of public health It is, therefore, narrower than the customary term "medical statistics", which embraces, for example, statistical experimentation in clinical and laboratory research It is wider than "vital statistics", which is merely one aspect of a public-health statistician's domain Dr Swaroop is particularly concerned that the experience of workers in countries where statistical services are highly developed shall be made available to those working in a much more difficult environment in the newly developing countries In this task his experience at W H O is invaluable, and a useful feature of his book is that it forms a guide to the many W H O. publications on problems of classification, nomenclature, and so on

Dr Swaroop discusses many practical and administrative points He does not delve deeply into vital statistics and hardly refers to the methodology of mathematical statistics, these topics are, of course, adequately covered by many other books The style seems at times a little stiff, probably because of the author's fondness for lists of precepts and principles which, excellent though they are, hardly make for compulsive reading Dr Swaroop has, however, written a book of unique interest, which will be widely referred to throughout the world

Lymphocytes and Mast Cells

MARGARET A KELSALL, PH D, biology research service laboratories, University of Colorado, EDWARD D CRABB, PH D, professor of biology, University of Colorado London Baillière, Tindall, & Cox 1959 Pp 399 64*s*

To the clinician or pathologist it is not very obvious why lymphocytes and mast cells should be grouped together The biologist looks on them, and the plasma cells, as free or independent connective-tissue cells having "functions in supplying nutritive materials and in regulating protein metabolism" These cells are called "trephocytes" (feeding cells) since they exist primarily for the benefit of other cells The approach in this book is histochemical and biochemical, and those not familiar with these areas will be astonished to find how much information has been accumulated about lymphocytes, plasma cells, and mast cells There is much material of direct interest to pathologists—for instance, the part played by these cells in normal healing Mast cells release histamine and heparin to produce hyperæmia and increased capillary permeability, lymphocytes and plasma cells release concentrated nucleoproteins for use by the other cells Textbooks of hæmatology may still find the function of the lymphocyte obscure Kelsall and Crabb are in no doubt that they synthesise and store nucleoproteins for use by other cells and provide energy for synthetic processes, they are also a source of minerals, particularly potassium

The first chapters deal with the distribution and "interrelationships" of mast cells and lymphocytes, the effect of mast-cell products on capillary permeability and the importance of heparin, histamine, and hyaluronic acid are considered in detail Then follow chapters on the minute anatomy and biochemical changes of cells in the thymus, spleen, bone-marrow, and intestinal lymphoid tissue Finally there is a long chapter on the histochemistry of inflammation and wound healing The bibliography contains no less than 1142 references, most of them published in the past ten years

The book is mainly a compilation of sometimes contradictory facts, with some attempt at assessment of their relative importance Summaries at the ends of the chapters would have helped, and it is often hard to follow the line of argument through the mass of detail Much of this information relates to observations and experiments on animals of many species, some observations are on human tissues Fortunately a good index enables specific points to be easily found, so that this in many ways unique volume is well worth a place in the reference libraries of pathology, hæmatology, and biochemistry departments

Newer Virus Diseases

Clinical Differentiation of Acute Respiratory Infections JOHN M ADAMS, M D, PH D, professor and chairman, department of pediatrics, school of medicine, University of California, Los Angeles New York and London Macmillan Company of New York 1960 Pp 292 40*s*

THIS book is more adequately described by its subtitle than by the misleading main title It deals with acute respiratory disease from an ætiological viewpoint, with a particularly comprehensive account of the viruses (including most of the more recently discovered agents except those recovered from common colds) and a perfunctory account of the bacteria and fungi Dr Adams has tried to delineate the clinical and epidemiological features which enable a specific diagnosis to be made without resort to elaborate tests Unfortunately, at present at least, rather little can be done other than to enumerate the ætiological agents and note the difficulty of distinguishing with certainty between them on clinical grounds alone Resort must be had to laboratory tests, and an ætiological diagnosis, despite the author's hopes, does not greatly affect the management or outcome of the disease The value of ætiological studies lies mainly in the prospect they offer of controlling respiratory disease in the future rather than for the management of the disease in the individual patient

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Clinical Tropical Diseases (2nd ed Oxford *Blackwell* Scientific Publications 1960 Pp 546 52*s* 6*d*)—In the seven years since this book by Dr A R D Adams and Prof B G Maegraith was first published it has established itself as a firm favourite among the medium-size works on tropical diseases Its general purpose is that of a practical guide to the everyday problems of diagnosis and management of patients in the tropics The teaching therefore is straightforward and dogmatic, and no references to the literature are included As is to be expected in a practical guide, personal preferences receive prominence in the management and treatment of some diseases, especially intestinal amœbiasis For the new edition, the sections on sickle-cell anæmia and inherited hæmoglobin abnormalities and on nutrition have been enlarged and a new section on epidemic hæmorrhagic fever has been introduced, but the size has been increased by only 32 pages Up to date and eminently practical, this work is assured, and worthily so, of a renewed period of success

THE LANCET

LONDON 22 OCTOBER 1960

Worth its Weight?

WHEN the probing beam of statistical trial is swung from new drugs to old, a testing time arrives for long-established impressions and perhaps some prejudices Taking time off from comparisons of steroids with analgesics, rheumatologists have turned their attention to gold salts, which have been used against rheumatoid arthritis for more than thirty years [1-5] but have never been universally accepted as effective or as reasonably safe. It may seem surprising that a definitive clinical trial of gold was not completed long ago, but the Empire Rheumatism Council, which has now reported its findings,[6] was unable to discover any assessment which fully satisfied today's strict requirements for a statistically controlled trial No earlier investigators had assembled treated and untreated groups balanced for sex, age, and duration of disease, had arranged that both groups should receive a course of injections, and had ensured that the identity of the injected material should be unknown to both patient and physician Many previous investigations fulfilled some of these requirements—notably an earlier trial planned by the same body but reduced in size by the war and completed in one centre by FRASER [7] Treatment comprised ten injections of 100 mg of sodium aurothiomalate, and at the end of a year more treated patients than controls were in better condition. Among other trials, some suggested that treatment with gold was of value,[8-11] while others did not [12 13]

The recent Empire Rheumatism Council trial involved twenty-four centres and 199 patients All patients had active rheumatoid arthritis of one to five years' duration, were between the ages of 20 and 64, and had not received gold at any time nor recent treatment with a steroid or chloroquine The standard course of treatment was 1 0 g of sodium aurothiomalate divided into twenty weekly injections Patients in the control group were given twenty injections totalling 0 01 mg of the same gold salt—the comparison being, therefore, between a total dose within the arbitrarily accepted therapeutic range and a very small dose, unlikely to exert any measurable effect All patients were given simple supportive treatment—rest, splints, aspirin, and physiotherapy Detailed assessments were made at intervals, the last about twelve months after the last injection

The results were clearly in favour of the full treatment from the third month after starting treatment Functional capacity, subjective fitness, and strength of grip improved more than in the control group, and this improvement was reflected in a smaller consumption of analgesic tablets, a greater rise in hæmoglobin level, and a more pronounced fall in erythrocyte-sedimentation rate On the other hand, the treatment had no detectable effect on the advance of erosive lesions measured radiographically This may have been due partly to the development or enlargement of lesions in the early weeks, before treatment had established its full effect, and it might have been interesting to compare films taken at the third month and a year later That the advance of lesions can be retarded by therapy was clearly shown in an earlier assessment of treatment with prednisolone [14]

And what of the cost in toxic effects? Many clinicians regard gold salts as too dangerous to administer, but those responsible for the present trial did not rate the incidence of untoward reactions as unduly high Of the 99 patients in the "treated" group dermatitis developed in 21, but this was severe in only 4, there were 3 cases of stomatitis and 2 of purpura Mild dermatitis occurred in 7 control patients and stomatitis in 2 Albuminuria was detected at some time in 4 cases, but was almost as common in the controls There was 1 death among the treated patients—of a man who developed dermatitis and died several months later of pneumonia complicating chronic bronchitis, gold was thought not to have contributed to his death Though not by any means negligible, this toll of toxic effects is hardly sufficient to condemn gold therapy, and the availability of dimercaprol for treating dermatitis and of steroids for the management of purpura has made these complications somewhat less formidable

The questions which any controlled therapeutic trial sets out to answer are necessarily limited This trial has established that a standard course of injections, modified only if toxic symptoms develop, produces a measurable improvement more often than a series of injections of the same material in minute doses, and that this improvement is still evident a year after the last injection Many clinical impressions, part of the folk-lore of gold therapy, could not be tested Will the treated patients continue to fare better? Earlier experience [15 16] suggests that after some years have elapsed patients initially treated with gold are in no better shape than those not so treated—and indeed in the present trial the margin between the two groups, measured in terms of subjective wellbeing and erythrocyte-sedimentation rate, was narrowing by the final assessment. More information on this point may emerge in a second report to be published when the patients have been examined two years after the end of treatment Is gold less effective when used for the second time? Again clinical impression maintains that this is so Can the results of treatment be improved by

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[9] Waine, H., Baker, F , Mettier, S R *Calif med J* 1947, 66, 295
[10] Adams, C. H., Cecil, R L *Ann intern Med* 1950, 33, 163
[11] Lockie, L. M , Norcross, B M , Riordan, D J *J Amer med Ass* 1958, 167, 1204
[12] Merliss R. R., Axelrod, B , Fineberg, J , Melnik, M *Ann intern Med* 1951, 35, 352.
[13] Brown, R. A P , Currie, J P *Brit med J* 1953, i, 916
[14] Joint Committee of the Medical Research Council and Nuffield Foundation *Ann rheum Dis* 1959, 18, 173
[15] Ragan, C. *Bull N Y Acad Med* 1951, 27, 63
[16] Snorrason, E *Acta med scand* 1952, 142, 249

tailoring the dose in some way to fit individual cases—perhaps by pressing on beyond the customary cumulative total dose as long as the erythrocyte-sedimentation rate remains high, or by instituting maintenance doses at longer intervals after the end of the intensive course? Is it true that toxic reactions are more liable to develop when the erythrocyte-sedimentation rate is low? On this last point the only information in the recent trial is that severe dermatitis developed in 2 cases when the rate was high. Until more is known of the duration of improvement and the possibility of prolonging it by some modification of the programme of treatment, the expediency of exposing patients to the undoubted risks must remain uncertain But the Empire Rheumatism Council has at any rate provided at last a firm foundation of established fact on which further exploration can be confidently based

Besides stimulating further work on treatment with gold salts, these results should lead to fresh efforts to discover their mode of action This will be no easy task for investigators dealing with a disease of unknown pathogenesis and a therapeutic agent capable, among other actions, of influencing several enzyme systems That the action of gold, transient though it may prove to be, is yet fundamental is suggested by the interesting observation that the titre of the rheumatoid serum factor tended to fall in the treated patients—an effect shared possibly with chloroquine but not with steroids

Fresh Thoughts on Food

Mr JAMES FERGUSON, the sanitary inspector for Aberdeenshire, has asked a question which is as important to ratepayers as it is to his profession and to ours[1] Of all the many samples of food and drink collected and analysed at great expense by the sanitary authorities, how many are found to contain deleterious materials such as to affect human health in any degree whatsoever? The procedure in England and Wales is not identical with that in Scotland, but the same question might well be asked by any health committee in Great Britain Nobody is likely to quarrel with the two assumptions which underlie the general practice (1) that the laboratory alone can show that food or drink is dangerous to the health of the consumer, and (2) that the more sampling and testing is done the safer we shall be But, though some authorities sample far more than others, the process can never be inclusive no-one would suggest that all foods should be tested for all poisons The choice of samples and the tests to which these are submitted have to be justified, and Mr FERGUSON has done good service in raising these questions for debate.

There are clearly good reasons for statutory limits to the amount of chemical or radioactive poisons in foodstuffs, and the health inspector must be prepared both for familiar and for new and unheralded dangers —e g , the presence of organic phosphates (used as pesticides) on imported fruit But do we need so many prosecutions for a deficiency of meat in sausages? It may please the public to know that the wicked butcher has been fined for depriving his customer of 5% of the pig meat for which he had paid, but the damage to health is nil Similarly, to sell whisky containing methyl alcohol is to endanger the public health, but one could argue that whisky containing too little alcohol of any kind is probably to the buyer's ultimate benefit At the time when most milk was produced and sold without regard for common cleanliness it was an administrative advantage to have a quantitative measure of keeping quality, and the housewife has never known what she owes to the methylene-blue test But to associate this in any rational way with public health is not easy So far from being deleterious, sour milk is highly recommended by some of our colleagues there is even evidence that the multiplication of the souring bacteria is antagonistic to the production of staphylococcal enterotoxin in milk[2] Some food is condemned on the mere presence of a pathogenic organism A single tubercle bacillus in a milk sample is enough to damn it, but in point of fact the many weary hours and many thousands of guineapigs spent in detecting tuberculous milk have had less effect on bovine tuberculosis in man than has the widespread pasteurisation instituted as much for commercial as for hygienic reasons That this disease is now on the verge of extinction is due to our veterinary colleagues and the spending of £130 million "Fæcal coli", too, would be most undesirable in milk—if they all came from the human bowel Prima facie, the presence of a single salmonella is enough to label food as unfit for human consumption, but whether human disease results will depend on whether there are 10 or 10^8 organisms per gramme, and whether the menstruum is oatmeal or caviare.

How much of any article of food should be sampled, and how frequently, is a statistical problem of great complexity which has had almost no attention Whereas 100 ml taken from many gallons of well-mixed milk gives a reasonable sample, to make certain that a bag of dried egg contains no salmonellæ at all probably means "sampling" the whole bag Is 1 lb of sausages enough to tell us with reasonable certainty that a whole day's output from the factory is free from pathogenic bacteria and conforms to the statutory requirements for meat content? Nobody knows The Metropolitan Water Board samples much of its produce daily some water undertakings sample once a month without disaster—so far The sampling of food and drink depends in fact mostly on habit and convenience, and not much on any quantitative reckoning of the possible danger to the public health

Whether the sampling of food and drink as done today affects the public health is part of a larger question which cannot be answered in any simple fashion Many measures taken in the name of hygiene seem rational enough, but their value has never been estimated quantitatively, as was, for instance, immunisation against diphtheria Some can never be submitted to such a stringent test, but the effect of some others could well be measured objectively For example, has the provision of new equipment and new communal kitchens altered the incidence of food-poisoning in schools? Has the sampling and testing of ice-cream been of demonstrable benefit to the public health?

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[1] *Scotsman*, Sept 7, 1960

[2] Jones, A C., King, G J C, Fennell, H Stone, D *Mon Bull Minist Hlth Lab Serv* 1957, 16, 109

When the late Sir JAMES SPENCE suggested that the school medical service did not perhaps do all that it set out to do he ruffled a good many feathers It would be a pity if Mr FERGUSON's remarks have the same reception In the process of time (and often by accident) duties have been unloaded on to the health inspector's shoulders which have very little to do with health in any way Simultaneously our conceptions of the cause and prevention of disease have changed, yet statements are made in public, and even in the courts of law, which suggest that disease is due to dirt and nasty smells Is a pie with a florid growth of *Aspergillus niger* between meat and pastry unfit for human consumption? It depends how hungry you are Tentatively, we suggest that the future of environmental hygiene lies in planned operational research, in a new definition of the main dangers to health, in an assessment of their real prevalence, and in fresh thoughts on their detection by simple and certain methods

Corticosteroids for Infections

WHY corticosteroids sometimes exert a profoundly harmful effect on the course of an infection is undecided The cause can hardly be a stimulant effect on the growth of the infective agent, for this would imply a similar metabolic response by such diverse microorganisms as fungi, protozoa, bacteria, rickettsiæ, and viruses, all of which have been shown to be affected by corticosteroids, and if this were indeed the case the principle would certainly have been adopted in diagnostic bacteriology for culturing organisms more speedily It is likelier that the infective agent gains a firmer hold and spreads because corticosteroids suppress the host defence mechanisms by affecting either circulating antibody or the cells themselves Cortisone interferes with the rise in titre of circulating antibody but does not alter the rate at which administered antibody disappears[1] This suggests impairment of antibody synthesis—an explanation which can hardly account for the clinical changes which may take place within a day of starting to administer steroids, or for the increased virus multiplication in cortisone-treated chick embryos devoid of antibody[2] Action at cellular level is more probable, and would explain the well-known anti-inflammatory effect of cortisone not only in infections but also in collagen disorders and hypersensitivity reactions By means of the rabbit-ear chamber technique, EBERT and WISSLER demonstrated that cortisone fundamentally alters the vascular and cellular factors in inflammation Capillary and arteriolar tone is increased, endothelial swelling is reduced, permeability to plasma-proteins is diminished, and the cells in the inflammatory exudate are changed While these modifications may be beneficial in collagen or hypersensitivity disorders, they can contribute adversely to inflammation due to infection, by preventing adequate phagocytosis, causing further necrosis or caseation, and hindering the normal development of granulation tissue and of healing

Some would regard these dangers as sufficient to rule out the use of corticosteroids in any infection, and this would be a sound policy were it not that nowadays increasing numbers of patients are already receiving lengthy courses of corticosteroids for other reasons. When these patients contract infections, corticosteroids need to be given in increased dosage rather than discontinued SKANSE and MIORNER,[4] for example, showed that the mortality from Asian influenza in Malmo was highest among those with uncontrolled adrenocortical disease Thus no absolute prohibition on the use of corticosteroids in the management of infections is feasible Furthermore, paradoxical though it may seem, the patient with Addison's disease who used to be susceptible to infection is now well controlled and free from infection despite continuous treatment with steroids Moreover in the past decade the deliberate use of these potentially dangerous drugs in overwhelming infections, unassociated with Addison's disease, has been found to result sometimes in prompt and dramatic improvement which persists long enough for antibiotics to take effect "Buying time"[5] in this way seems justifiable when death is the almost certain alternative For the successful management of adrenal failure associated with fulminating meningococcal infections, early intravenous administration of hydrocortisone, besides sulphonamides, is essential A commoner problem is to decide when a drug of the cortisone group should be combined with sulphonamides in the therapy of the less malignant meningococcal infections KINSELL and JAHN[6] recommended routine combined therapy for all patients with meningococcal septicæmia, but LEPPER and SPIES[7] were unable to confirm that such a regime had definite advantages in septicæmic patients with or without meningococcal meningitis The sulphonamides, administered intravenously as well as orally, are usually sufficient, but the use of steroids in addition should be considered if signs of impending adrenal failure appear

Corticosteroids have rapidly relieved fever and toxæmia in brucellosis,[8] typhoid fever,[9 10] and Rocky Mountain spotted fever[11], and carefully controlled trials have shown a similar pattern of response in pneumococcal pneumonia[12 13] WAGNER et al[12] compared the course in 61 penicillin-treated pneumococcal pneumonias with that in 52 patients who also had hydrocortisone orally for five days A more rapid subsidence of fever and relief of symptoms distinguished the hormone-treated group, although occasional recurrences followed withdrawal of hydrocortisone No such recurrence or "rebound" of fever was observed on withdrawal of hormone in a controlled blind trial by Kirby et al [13] on 42 cases of pneumococcal pneumonia All the patients received 2 g of tetracycline daily, and half of them also received 32 mg of methyl prednisolone on the first day, 16 mg on the second and third days, and 8 mg on the fourth day Complications directly attributable to methyl prednisolone were not observed Rapid defervescence in the steroid-treated group was the most noticeable feature of the study, at the end of twenty-four hours three-quarters of the steroid-treated group were afebrile, compared with a third of the control group receiving tetracycline alone. At the end of forty-eight hours, nine-tenths of those receiving steroids were afebrile, compared with only half the control group Otherwise, there were no significant differences in the laboratory findings or in the resolution of the pneumonia, and complications were few and slight in both groups Kirby et al conclude that corticosteroids are not indicated in uncomplicated pneumonia, but that they may be of value in the highly febrile toxic patient Aspirin has long held pride of place as a more acceptable alternative to the potentially dangerous steroids in the symptomatic treatment of pneumonia, and a comparison of these two agents in conjunction with penicillin would be instructive It seems likely that the antipyretic effect of steroids would be greater This can be inferred from a controlled study by Petersdorf et al [14] who compared aspirin and a placebo in 67 patients with pneumococcal pneumonia, all of whom were treated with penicillin In the group who received aspirin fever was not controlled more rapidly, and the only real difference in this group was greater symptomatic relief in the first twenty-four hours of treatment

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[1] Fischel, E. E., Stoerk, H C., Bjorneboe, M *Proc Soc exp Biol, N Y* 1951, 77, 111

[2] Kilbourne, E. D *J exp Med* 1955, 101, 437

[3] Ebert, R H, Wissler, R W *J Lab clin Med* 1951, 38, 497, 511

[4] Skanse, B, Miörner, G *Lancet*, 1959, i, 1121

[5] Jahn, J P, Boling, L, Meagher, T R, Peterson, H H, Thomas, G, Fisher, B M, Thill, A E, Leovy, W A., Balch, H E., Kinsell, L W *J Pediat* 1954, 44, 640

[6] Kinsell, L. W, Jahn, J P *A.M.A Arch intern Med* 1955, 96, 418

[7] Lepper, M H, Spies, H W *in* Antibiotics Annual 1956–57, p 447 New York, 1957

[8] Magill, G B, Killough, J H, Said, S I *Amer J Med* 1954, 16 810

[9] Woodward, T E, Hall, H E., Diaz Rivera, R, Hightower, J A, Martinez, E., Parker, R T *Ann intern Med* 1951, 34, 10

[10] Smadel, J E., Ley, H L., Diercks, F H *ibid* p 1

[11] Workman, J B, Hightower, J A, Borges, F J, Furman, J E., Parker, R. T *New Engl J Med* 1952, 246 962

[12] Wagner, H N, Jr, Bennett, I L., Jr, Lassagna, L., Cluff, L. E., Rosenthal, M E., Minick, G S *Bull Johns Hopk Hosp* 1956, 98, 197

[13] Kirby, J C., Jr, Polis, G, Romansky, M J *Amer J med Sci* 1960, 240, 30

Initial clinical improvement is hastened by giving steroids with antibiotics in tuberculosis [15], combined therapy, although not advisable as a routine, may be particularly useful when the patient is severely ill and toxic, when the pleura or meninges are involved,[16 17] or for controlling hypersensitivity reactions [18] It remains to be seen whether steroids can conserve lung function and prevent long-term chronic respiratory disability

In virus infections clinicians have been reluctant to give steroids, because no antibiotics are available as "insurance cover" and because of the reported hazards Haggerty and Eley,[19] for instance, drew attention to 12 fatalities in children who were receiving corticosteroids at the time of exposure to chickenpox None the less, corticosteroids have sometimes proved helpful in other virus infections such as infective hepatitis, infectious mononucleosis, mumps, and influenza In cases of virus hepatitis corticosteroids bring about a rapid fall in the serum-bilirubin level,[20] although serial aspiration liver biopsy studies have revealed no significant change in the underlying disease process [21] Corticosteroid therapy is indicated for the fulminating condition bordering on hepatic coma, for hepatitis complicated by long-continued obstructive jaundice, and for relapses of the disease Steroids are not indicated in ordinary uncomplicated hepatitis In infectious mononucleosis corticosteroids are rarely indicated,[22] but they may be valuable when the disease is complicated by profound toxæmia, severe hepatic involvement, or encephalomyelitis Acute disseminated encephalomyelitis following measles, chickenpox, rubella, or vaccination against smallpox or rabies may be favourably influenced by steroid therapy, which diminishes the initial mesodermal inflammatory reaction but does not affect established axonal damage The response of these acute neurological disorders to cortisone supports the hypothesis that they are due to anaphylactic sensitisation [23 24]

When inflammatory exudate causes congestion in an unyielding space, the resulting pain and tenderness cause distress By reducing inflammation, the corticosteroids can be expected to relieve discomfort Such relief has been achieved both in mumps orchitis [25] and in neural leprosy [26] As regards more chronic conditions arising from virus infections Mickerson [27] has suggested that corticosteroid therapy may be beneficial in influenzal debility states

The evaluation of these drugs in infections requires controlled trials But much can be learnt from the reports of observant clinicians called on to treat winter infections among patients receiving steroids for other reasons In the antibiotic age the treatment of infections has so far been more effective than ever before Will this advantage be maintained in the corticosteroid era?

Nightingale and Lister

If they are to benefit from their increasing complexity, developing organisms must establish adequate pathways for sensory messages The hospital bodies created under the National Health Service are faced with the need for this biological adjustment, and, perhaps because so many of their nerve-endings take the form of a committee, have not yet been entirely successful in making it As a result, important parts of a hospital are still too often left in nescient isolation

Not long ago Dr Godber [28] suggested that the improvement of communications between the hospital and the family doctor could be the most urgent problem of the next ten years Smaller, but important to the internal economy of a hospital, can be a gap between the administrators and the matron In the voluntary hospitals, from Miss Nightingale's days until 1948, the matron was recognised by the governing body, as well as the medical staff, as their partner In the N H S, perhaps because of Miss NIGHTINGALE's regrettable absence, the matron's position, as King Edward's Hospital Fund[29] once put it, "often falls far short of the part assigned to her in the Nightingale pattern" As long ago as 1954 the Bradbeer Committee[30] urged that she should be directly responsible to the governing body of her group of hospitals and have direct access to it Since then the Ministry of Health have several times[31] reminded hospital authorities that matrons should be kept informed about matters of policy and should attend meetings of house committees, hospital management committees, and boards of governors, and should have an opportunity to comment on developments and changes of policy Many hospitals have no doubt already profited by this good advice that there are exceptions is shown by the Ministry's persistence in offering it. Last year the nursing committee appointed by the Northern Ireland Hospitals Authority[32] was still concerned about the matron's lack of administrative contacts As they rightly suggest, "it is unreasonable to expect a matron to administer satisfactorily if she is not fully informed of the policy of management and is not aware of the reasons that have justified the policy"

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[14] Petersdorf, R G, Cluff, L E, Hoeprich, P D, Hopkins, F T, McCann, W P *Bull Johns Hopk Hosp* 1957, 101, 1
[15] Houghton, L E *Lancet*, 1954, i, 595 Tuberculosis Society of Scotland *Brit med J* 1957, ii, 1131
[16] Turiaf, J, Marland, P *Bull Soc méd Hôp Paris*, 1955, 29, 1174
[17] See *Lancet*, 1959, i, 1135
[18] Houghton, L E *ibid* 1954, i, 595
[19] Haggerty, R J, Eley, R C *Pediatrics*, 1956, 18, 160
[20] Evans, A S, Sprinz, H, Nelson, R S *Ann intern Med* 1953, 38, 1134
[21] Shaldon, S, Sherlock, S *Brit med J* 1957, ii, 734
[22] Mason, R, Adams, E K. *Amer J med Sci* 1958, 236, 447
[23] Selling, B, Meilman, E *New Engl J Med* 1955, 253, 275
[24] Miller, H G, Stanton, J B, Gibbons, J L *Brit med J* 1957, i, 668
[25] Petersdorf, R G, Bennett, I L, Jr *Arch intern Med* 1957, 99, 222
[26] Jopling, W H, Cochrane, R G *Leprosy Rev* 1957, 28, 5
[27] Mickerson, J N *Lancet*, 1959, i, 1118
[28] Godber, G E *ibid* 1959, ii, 224

But effective administration usually rests on consultation and discussion between colleagues, and even the Bradbeer Committee said nothing about the need for communication between the matron and the medical staff True, nearly every hospital has a nursing as well as a medical committee, but they are not comparable. The nursing committee ranges from the "non-professional" (largely made up of members of the management committee and a few other lay people from the neighbourhood, with the matron very much in attendance) to the "purely professional" (when the sisters meet with the matron in the chair) But, whatever the pattern adopted, the nursing committee seldom has contact with the medical committee The possibility that an "intraprofessional" committee might be a useful device is suggested by the following examples of administrative unorthodoxy sent us by a Scottish correspondent

Hospital A is hard to get at and used to have a large poor-law institution in its grounds Its administrators, keen though they were to build it up, wished to avoid too many meetings, so they made one committee for the medical and nursing services Matron is a member of this along with members of the hospital staff and laymen She also attends the meetings of the full board of management. As a result of this arrangement, there is a lively but always helpful exchange of points of view, and the medical and nursing staffs appreciate each others' problems and approaches to the patients' welfare

Hospital B is a fine old teaching establishment, now in need of rebuilding but rich in high dames, old boys, and leading lights of the profession Matron sits on the nursing committee, which is rather infrequently attended by the member of the medical staff elected to it. She is not a member of the medical committee and she is not invited to attend meetings of the board Not long ago this hospital set up a control-of-infection committee and wisely made Matron a member of it Here, at last, real exchanges of view between the Matron and the doctors have begun to show useful results

These two successful Northern experiments lead our correspondent to ask whether the medical and nursing services should not meet more often round the committee table At present their usual point of contact is the patient, and admittedly he is the raison-d'être of both But the bedside is not the ideal place for discussing principles or plans for the hospital as a whole An atmosphere of reasonable and regular consultation should be developed, for without it there is needless multiplication of stupidities, obstinacies, and misunderstandings, while efforts to improve the medical and nursing care of the patients are often frustrated Trust and cooperation are not best fostered by ingenious and numerous regulations (which in practice the needs of the sick are apt to overrule), but regular meetings between matron and doctors would often save tempers as well as time and do much to reconcile the spiritual descendants of NIGHTINGALE and of LISTER

Annotations

EARLY GRAFTING IN BURNS

No surgical problem has been more intensively studied than the management of the burned patient The central question remains how best to repair the damaged "skin envelope" of the body with the least delay A fit young patient, with a full-thickness skin loss of 25% of the total surface area should survive Yet in such a case an area of about 500 sq in must be grafted, and the recipient plus donor sites will total 50% of the entire skin surface, and, if the back and front of the trunk are grafted at one session, there will be a poor "take" in the zones exposed to pressure A further difficulty is that deeply burned areas cannot be prepared for grafting within three (or at the very least two) weeks, except by surgical excision This procedure has been fully explored and frankly reported in a paper by Jackson et al,[1] of the Medical Research Council Burns Unit at Birmingham In assessing their findings, we may accept that no other surgical centre is likelier to have mastered the problems of blood-loss, of cross-infection, and of the strenuous time-consuming demands of massive grafting

In summary these workers found that excision and grafting of 20–30% of the body surface can be carried out on the day of injury, without increased risk to life—but only with adequate safeguards The special dangers include latent oligæmia, hidden red-blood-cell destruction, serious postoperative oozing due to an unexplained tendency to bleed, and infection of the grafted area when ungrafted burns are adjacent Some of these dangers can be anticipated and mitigated if the surgeon is watchful for example, the uppermost areas, in relation to the patient's position in bed, should be grafted first

Jackson and his coworkers do not advocate early excision and grafting as a routine procedure, and they admit that it demands more experience and involves more trouble than conventional techniques In their view the strongest indication is the extensive burn with deep involvement of the subcutaneous tissues, since in such a case natural separation of sloughs often takes six weeks (A really satisfactory desloughing agent might advance the treatment of burns almost as much as elimination of the homograft barrier)

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[29] Evidence to Bradbeer Committee London, 1951

[30] Bradbeer Committee Internal Administration of Hospitals H M Stationery Office 1954

[31] R.H.B.(49)25 R.H.B.(49)143, H.M.(54)4, H.M.(59)21

[32] Report of Nursing Committee Belfast, 1959

[1] Jackson D, Topley, E., Cason, J S, Lowbury, E. J L. *Ann Surg* 1960, 152, 167

This technique may call for massive manœuvres For example, the blood-loss in the first twenty-four hours of a 30% burn treated by excision may amount to 112% of the normal number of circulating red cells Accordingly, transfusion of 6 pints during a two-hour operation is sometimes necessary Again, if the grafts average 8 × 4 in in size, at least ten such sheets of skin would be needed for an adult with deep burns involving 30% of the surface area Attempts have been made to reduce the demand by means of " postage-stamp " grafts, but here the gain in cover is heavily offset by delayed healing, and the final appearance is often patchy. Similarly alternate strips of autografts and homografts are sometimes life-saving, but, except in the most favourable circumstances, further autografts will be needed later An improved " take " would increase the justification for early excision, and Cason and Lowbury,[2] of the same unit, suggest that a cream containing neomycin, chlorhexidine, and polymyxin B, applied as a dressing for grafts, may help to diminish early postoperative infection and consequent loss of grafts.

THE RETINA IN SEVERE HÆMORRHAGE

THE flood of medical discovery rises so quickly that it is not surprising that many old but important facts become submerged The effects of severe hæmorrhage on vision provide a case in point, and Pears and Pickering [3] have done a useful service in reporting instances of two kinds of visual change which were well known fifty years ago but have since been largely forgotten

The first consists in sudden loss of vision, usually after a large hæmorrhage Pears and Pickering observed the retina in one such case from the onset of the blindness, which was unilateral The earliest change was enlargement of the retinal veins on the second day, followed later by swelling of the disc and eventually by optic atrophy This is a rare condition and is usually preceded or accompanied by loss of consciousness and convulsions—that is, by symptoms of cerebral anoxia Death of the ganglion cells may of course be a direct result of anoxia, but the delayed onset of blindness, in some cases, and the papillœdema suggest that the major lesion may be in the optic nerve itself, in which histological abnormalities have in fact been described [4, 5] Although lack of red corpuscles may play some part in causing these changes, the sudden fall of blood-pressure seems likely to be more important Unilateral blindness has been observed to follow the administration of hypotensive agents in anæsthesia Goldsmith and Hewer [6] suspected occlusion of the central retinal artery by spasm, while Gillan [7] suggested that external pressure on the eyeball may be a factor

The second and commoner complication of hæmorrhage is a form of neuroretinopathy which closely resembles that found in malignant hypertension Pears and Pickering describe several such cases In this condition there is little visual disturbance apart from occasional blurring of vision, but papillœdema is common and focal hæmorrhages and exudates are present These usually resolve eventually without leaving any obvious abnormality It is therefore unlikely that any permanent damage is caused, and the changes seem to be due to escape of blood from abnormally permeable vessel walls Although this could conceivably be a result of anæmia, which is known to cause similar changes, the lesions seem to be more closely related to sudden falls in blood-pressure. The resemblance to the retinopathy of malignant hypertension is of particular interest In both conditions, especially the latter, there is evidence of raised intracranial pressure Clinical observations throw little or no light on the cause of this raised pressure In experimental malignant hypertension gross or even fatal cerebral œdema is regularly present, and it is possible but not proven that a similar cerebral œdema may account for the swelling of the nerve head The retinal hæmorrhage and exudates cannot in either case be attributed to papillœdema, and the presence of essentially similar lesions in two unrelated diseases suggests that some common factor—probably focal ischæmic anoxia—is concerned In experimental malignant hypertension Byrom [8] has demonstrated focal exudates and hæmorrhage in both the brain and the retina, and has shown that these are related to reversible constriction of small arteries If the focal retinal lesions in cases of hæmorrhage are also anoxic in origin, the simplest explanation is that when the arterial system is suddenly depleted of blood the critical closing pressure is reached and isolated segments of small arteries are temporarily closed There is no direct clinical evidence to support this explanation, which does not readily account for the appearance of lesions, in some cases, some days after the hæmorrhage has apparently been corrected But, as Pears and Pickering point out, this may simply mean that retinal damage of this kind does not always become immediately visible

BROADER MEDICAL TEACHING

DURING the past fifteen years most medical schools in this country have been much concerned to increase the students' awareness of social factors in disease The teaching of social and preventive medicine has been extended, and in many universities schemes of various kinds have been devised to widen the student's experience of medicine outside the teaching hospital Most students now have better opportunity than their immediate predecessors to see something of the social services in action, a large number are able to observe the family doctor at work, and some are incorporated for a short time into the functions of a health centre

There has been no intense controversy over these activities, and there seems to be general acceptance that to move along these lines is correct and necessary, now that more scientific medicine and more specialisation are making big changes in hospital practice It does not seem, however, that the educational objectives of any of the various schemes have been delineated very precisely Sometimes one and the same experience seems to be expected to serve many and varied purposes, ranging from the acquisition of a quantitative attitude of mind, through experience of the signs of early and trivial disease, to observation of " what the G P does "

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[2] Cason, J S, Lowbury, E J L *Lancet*, Sept 3, 1960, p 501
[3] Pears, M A, Pickering, G W *Quart J Med* 1960, 29, 153
[4] Ziegler, E *Beitr path Anat* 1887, 2, 361
[5] Goerlitz, M *Klin Mbl Augenheilk* 1920, 14, Beilage 3, p 3
[6] Goldsmith, A J B, Hewer, A J H *Brit med J* 1952, ii, 759
[7] Gillan, J C *Canad med Ass J* 1953, 69, 295
[8] Byrom, F B *in* Lectures on Scientific Basis of Medicine, vol 8 London (in the press)

Perhaps because of this absence of clear-cut objectives, little has been done to try to measure results Of particular interest, therefore, is the work of the University of Colorado Medical School, and in *Teaching Comprehensive Medical Care*[1] Hammond and Kern describe their evaluation of the effect on clinical students of attachment to the general medical clinic in Denver City Hospital. This clinic was started seven years ago as an innovation in medical care. It has provided a section of the indigent of Denver with full medical services, and to do so a large group of specialists and a full supporting cast of social workers of all kinds have been organised into a single team For five years half of each annual entry of clinical students has shared in the work of the clinic and been taught in it by members of its staff. For the same period a major and praiseworthy effort has been made to discover what effect this experience has had on these students, and why

Conscious of the present limited state of techniques for making such assessments, the authors are critical of both their methods and their results Yet both are worthy of careful study Even if no similar clinic could function in this country, there is no reason why we should not subject some of our newer teaching devices to similar scrutiny, particularly if they aim, as in Denver, to increase the students' knowledge and skill in medicine, psychology, and sociology, and to improve his attitude to all three It is possible that we would get rather similar results Already there is reason to suppose that our junior students are not sufficiently mature in medicine to benefit from much experience outside hospital. Meanwhile their seniors seem to judge the value of appointments (and thus decide the energy to be expended) more by the relevance they imagine them to have to final examinations than in terms of objectives stated by teachers In Denver senior students apparently felt obliged to learn data and techniques believed by them to be necessary for interns, and expected by them to be taught best in traditional appointments They tended therefore to resent the general medical clinic, but it is important to note that in fact those who passed through it gained no less medical knowledge and skill than did those who followed the traditional curriculum. It is also striking that in Denver a student's attitude towards psychology seems to depend more on his inherent personal interest in the subject than on his exposure to an experience intended to widen it. There is value to us too in the suggestion that closer contact with social services does not seem to increase their importance in the eyes of medical students

The University of Colorado's work, carried out with the assistance of the Commonwealth Fund of New York, is undoubtedly a valuable contribution to medical education and to our knowledge of how to study it. It suggests that specially contrived additional appointments may not achieve their educational purpose, if the remainder of the students' experience is spent in an atmosphere vaguely hostile to that purpose.

The report includes a timely reminder that, although a humanitarian outlook should condition the work of every doctor (and be acquired by every student), this is not the same thing as knowledge of human behaviour Such knowledge is not an attitude of mind but a body of experience and a growing series of techniques—both of which are of extreme importance to everyone in medicine, however humanitarian they may be by nature. If this body of knowledge has now reached the status of a scientific discipline, then students will be able to acquire it only by proper study of this discipline, beginning it at the same time as the other basic medical sciences If, however, this subject is still only in the stage of empiricism, then it is best not to conjure up special conditions for its study, but to leave the student to acquire what he can by seeing many patients (both inside and outside hospital) in the course of apprenticeships to wise and kindly doctors

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[1] Teaching Comprehensive Medical Care. By KENNETH R. HAMMOND and FRED KERN, Jr., M.D. Cambridge, Mass. Harvard University Press London Oxford University Press 1960 Pp 642. 80s

FATAL JELLYFISH STINGS

JELLYFISH stings are a common experience among holiday-makers throughout the world. The effects, though unpleasant, are short-lived, rarely serious, and never fatal—except in the tropical waters of north Australia and the western Pacific, where stings may rapidly result in death. Such stings have often been wrongly attributed to physalia, the Portuguese man-of-war, but increasing evidence points to a cubomedusa as the causal cœlenterate.[1] [2] These fatal stings are accompanied by weals and should not be confused with the *Irukandji* sting[3] in which local weals are absent but general symptoms of shock, vomiting, and violent cramp-like pains occur The cause of the *Irukandji* sting is unknown it is named after the tribe formerly inhabiting the north Queensland coast along which these non-fatal stings are incurred.

The cœlenterate phylum contains jellyfish, corals, and sea anemones, all of which have stinging capsules called nematocysts Structurally, cœlenterates are either polyps —cylindrical, usually fixed at one end, mouth with tentacles at the free end—or free-swimming or floating medusæ, which have bells with marginal tentacles Corals and sea anemones are exclusively polypoid (class anthozoa) but many cœlenterates alternate between polyp and medusa stages Jellyfish are classified as hydrozoa or scyphozoa Of the former class, physalia is a well-known example found in Atlantic, Mediterranean, and Indo-Pacific waters It is a colony of polyps and medusæ with a highly coloured airfloat. Despite this conspicuous appearance, no authentic record connecting it with fatal stings has been found.[4] The most important order in the scyphozoa is the cubomedusa ("sea wasps" or "box jellies"), so called because of the squarish or cuboidal bell A group of 1–15 tentacles hangs from each of the four corners The larger and multitentacled specimens are exclusively tropical. Another distinction from physalia is that they are difficult to see, being almost transparent in water

Nematocysts are minute capsules containing an intraverted hollow thread which, in response to a suitable stimulus, is everted. The thread of poisonous cœlenterates can penetrate, and when it is fully evaginated a toxin is injected. The nematocysts may be present both on the tentacles and on the bell. The structure of the nematocysts varies, that of the cubomedusa being quite distinctive from physalia.

Kingston and Southcott[5] now report two cases of fatal jellyfish stinging in north Queensland Red-brown skin weals were evident, and at necropsy acute pulmonary œdema was the principal macroscopic finding Histologically, nematocysts on the skin surface accurately matched those of the cubomedusæ *Chironex fleckeri* and *Chiropsalmus quadrigatus* Threads from these nematocysts were seen penetrating into the dermis, and severe degenerative changes in the malpighian layer were observed Research on the venom is proceeding,[6] but since victims usually die within a few minutes of the sting the prospects of successful treatment seem remote

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[2] Southcott, R. V. *ibid.* p 272.
[3] Flecker, H. *ibid* 1952, ii, 89
[4] Southcott, R. V. *Milit. Med.* 1959, 124, 569
[5] Kingston, C. W., Southcott, R. V. *Trans R Soc. trop Med. Hyg* 1960, 54, 373

DEPRESSION, ELECTROLYTES, AND E C T

THE crucial observation by Gjessing[7] that mental changes in periodic catatonia were accompanied (and could be influenced) by parallel alterations in nitrogen balance aroused hope that biochemical mechanisms would be revealed in less rare psychiatric syndromes Manic-depressive illness, by virtue of its frequency and often cyclic nature, was an obvious choice for study, but as Mayer-Gross[8] has pointed out, disappointingly little knowledge has been gathered Crammer,[9] among others, has recorded impressive changes in body-weight, water, and sodium accompanying depressive and manic phases, and Altschule et al[10] noted considerable retention of water and sodium in the 24 hours after electroconvulsive therapy (E C T) As an approach to a fundamental mechanism, however, this work has been called in question by the careful studies of Russell,[11] who submitted 15 severely depressed patients to precise calorie and electrolyte control throughout their course of treatment Retention of water and sodium after E C T was confirmed but occurred similarly when the procedure was repeated omitting the shock Russell attributes the electrolyte changes to the anxiety which precedes the treatment, though the atropine and thiopentone may have played a part But Brill et al[12] (on uncertain grounds) believe that the E C T procedure is of equal therapeutic value whether or not the shock is administered, and, if this is so, the electrolyte changes may still reflect true clinical improvement In Russell's 15 cases electrolyte retention after E C T tended to be greater in cases that responded well, though there were one or two notable exceptions The gain in body-weight which commonly accompanies recovery was shown here to depend on increased well-being and appetite, for it did not take place if calorie intake remained constant

The differences between these findings and those of others, notably of Crammer, may reflect differences in types of cases under study, for Crammer's were cyclical with spontaneous changes whereas Russell's were not Unlike other workers Gibbons,[13] who used the sensitive radioactive-isotope method, has shown a small daily loss of sodium (about 5 mEq) in most depressed patients during recovery

It remains to be shown definitely whether E C T is followed by a rise in electrolytes whereas the whole recovery process is accompanied by a gradual decline Such changes, if they exist, almost certainly depend on suprarenal activity, and thus studies of them are little more than skirmishes with the outposts of mood-controlling mechanisms But there are grounds for hoping that before long the battle will be carried closer to the headquarters

HYSTERECTOMY WITH OR WITHOUT OOPHORECTOMY?

IN cases of ovarian carcinoma, laparotomy often discloses widespread secondary deposits after only a few weeks of indefinite pain or abdominal distension This suggests that attention should be centred on prophylaxis, especially in women over 40 years of age. But how far should prophylaxis be carried?

Removal of both ovaries is not uncommon, often years before the expected time of the menopause, at hysterectomy in women of 40 or even younger But, as Schabort[1] points out, the value of oophorectomy in countering the risk of malignancy must be set against the physiological and psychological disadvantages of castration—disadvantages which hormone therapy and reasoned argument will not necessarily dispel The advocates of the radical approach maintain that the ovaries become functionless soon after hysterectomy, but Leverton[2] and Whitelaw[3] have advanced considerable evidence that some physiological ovarian function may continue for many years after hysterectomy, and that hysterectomy alone does not accelerate the menopausal phase, which takes place at the normal time for the individual, whatever the date of hysterectomy Further evidence of ovarian activity in the absence of the uterus is provided by those cases of congenital aplasia of the uterus in which laparotomy reveals active ovaries with graafian follicles and even corpora lutea Furthermore, Barr[4] has suggested that natural œstrogens play a part in lipoid metabolism, and that their removal increases the tendency to atherosclerosis—a tendency not necessarily reversed by œstrogen therapy

What in fact is the risk of malignancy in ovaries conserved at hysterectomy? Schabort concludes that Jeffcoate's[5] estimate is reasonable, and that the incidence of carcinoma in the ovaries after hysterectomy is of the order of 2 in 5000 Thus an active gynæcologist might in his professional lifetime find that in 2 of his cases carcinoma developed after hysterectomy By protracted and careful follow-up he might even detect the carcinoma in 1 of these in time for effective surgery, and thus 1 death must be measured against the disadvantages of castration in the remaining 4999 From the evidence assembled by Schabort the present trend towards conservation seems, on balance, justified As Patrick[6] has remarked, it is irrational to worry about leaving the ovary at abdominal hysterectomy, and yet to accept conservation as a rule when the approach is vaginal

More research is needed into the biochemistry and physiology of the menopause and into the question of whether artificial œstrogens or other measures can maintain the premenopausal state in the body as a whole after the ovaries have been removed Meanwhile there seems to be a strong case for conserving the ovaries in any woman who has not reached the menopause

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Special Articles

SUICIDE

THE INFLUENCE OF ORGANIC DISEASE

IAN STEWART
M.D. Leeds

CONSULTANT PATHOLOGIST
TO THE VICTORIA HOSPITAL, KEIGHLEY, YORKS

DETAILS of the physical illnesses which suicide victims have had are not readily accessible. The pathologist's report is lodged in the confidential files of the coroner's office, and the pathologist may or may not keep copies for his own information. The duties of the coroner are limited to the identification of the individual, and the ascertainment of the time, place, and manner of death. In his verbal summing-up he often refers to physical disabilities which may have contributed to the suicide, but this information is not included in the official verdict.

The influence of physical illness is further obscured by the almost invariable formula, "... while the balance of his mind was disturbed" or "... while of unsound mind". Derived from the labelling of suicide as a crime by both Church and State, they were introduced to circumvent the restrictions and penalties imposed on the dependants of the victims. These, fortunately, are in practice almost obsolete.

Because of these two factors suicide is now held by the lay public, and to a less extent by the medical profession, to result from disturbance of the mind alone. In a recent report (Capstick 1960) on the recognition of emotional disturbance and the prevention of suicide, no reference is made to organic disease. No-one would deny that psychiatric disturbance is the main antecedent of suicide, but, as the following figures show, organic disease does play a part in preparing the field for disaster. The cases I have examined in the Keighley area from September, 1952, to September, 1959, number a hundred and twenty-two. They may be classified into eleven groups.

GROUP 1. NO ORGANIC DISEASE FOUND 37 (30%)

These comprised twenty-one men, of average age 45 years, and sixteen women, whose ages averaged 56. Only one woman was less than 50, whereas twelve men were below 50.

GROUP 2. HYPERTENSION WITH CARDIAC HYPERTROPHY 33 (27%)

The moods of depression associated with hypertension and gross cardiac enlargement are familiar to the physician. There were eighteen men (average age 60 years), and fifteen women (average age 68). It is difficult to believe that a control group of this age, if it could be devised, would yield such a high proportion of patients with severe hypertension.

Various conditions were associated with the hypertension. Nine subjects had severe chronic nephritis, but the absence of this disease in the majority indicates that hypertension had developed recently and had been rapidly progressive. The hearts weighed 17–31 oz. Six subjects were grossly obese; two had recently had their gallbladders removed, and in one case the operation was immediately followed by a severe cerebral thrombosis, one man had a large gastric cancer causing pyloric obstruction, two had enlarged prostate glands with hypertrophic bladders, and one of them had recently undergone prostatectomy, one woman had a cortical adenoma of the adrenal, two men had almost complete occlusions of the left coronary artery, and one woman was a diabetic with a large [illegible].

GROUP 3. PEPTIC ULCER AND GASTRITIS 10 (8%)

Eight subjects had active gastric or duodenal ulceration; in some the ulcers were multiple, and in one burrowing deeply into the pancreas. Two men had very severe hypertrophic gastritis, which was probably alcoholic. In all these cases the disease may have been part of the nervous instability which led to suicide; but it is also possible that the continued pain and dyspepsia may, from fear of cancer or operation, have led to the ultimate depression.

In addition, one woman had severe anæmia and advanced pulmonary emphysema. One man had angulation of the spine from an old fracture, and was in constant pain; his right coronary artery was nearly blocked. Another woman was grossly obese, and another man had advanced pulmonary emphysema.

GROUP 4. GROSS OBESITY

Eleven women (9%) were of such physique that even the ascent of a short flight of stairs would be a major physical effort. In two the left coronary artery was nearly blocked, another had advanced fatty infiltration of the heart, and a fourth had fatty degeneration of the liver.

In the whole series there were twenty-one cases of gross obesity (17%). The severe restriction on mobility must have been a potent cause of depression in them all.

GROUP 5. THYROID DISORDERS

One woman with a symmetrical and massive non-toxic goitre was very obese, and two subjects had large and visible adenomas. The fourth had had a partial thyroidectomy some years previously, there were massive intrathoracic deposits and two cervical vertebræ were so far destroyed that death was imminent.

GROUP 6. GALLSTONES (8)

Five subjects were found to have gallstones, and three more had recently had operations for their removal. One old man with multiple stones had pronounced brown atrophy of the heart. Gallstones are a common accidental finding at necropsy, and it would be adventurous to suggest that gallbladder disorders are a common source of depression. But a physician I know who had repeatedly deferred the removal of his gall-bladder was inspired to have it done when he read my letter on the subject 3 years ago (Stewart 1957); he has recently written to say that his previous fits of depression have now disappeared.

GROUP 7. FATTY INFILTRATION OF HEART-MUSCLE (6)

None of these subjects was obese, and one was emaciated. One woman had the scars of several large cerebral thromboses, and her left coronary artery was nearly closed. This condition was seen in only one of the twenty-one cases of gross obesity previously described.

GROUP 8. MALIGNANT DISEASE (3)

One man was in the last stages of lung cancer, and one woman with a palliative colostomy had a rectal cancer which almost filled the pelvis. Another man had had the prostate and most of the bladder removed, rendering him permanently incontinent, and his liver was almost fully replaced by metastases.

GROUP 9. ANÆMIA (2)

One woman with a hæmoglobin level of 40% also had evidence of a severe cerebral thrombosis; the second had a hæmoglobin level of 50%. Another case has been mentioned previously.

GROUP 10. ADVANCED CORONARY DISEASE (3)

In these men the left coronary artery was nearly closed by fatty or calcareous deposit. In the whole series there were nine subjects in the final stages of coronary-artery disease.

GROUP 11

Two cases are not appropriate to the groups already described. One man was disabled by multiple sclerosis. The other, who had cut his wrists but only produced a moderate hæmorrhage, was found dead. At post-mortem his adrenal glands were five times the normal size. This man, in life, had avoided all forms of excitement, and he was thought to have died of adrenal excess as a result of the suicidal attempt

The general pattern in this series remains the same as in the sixty-five cases I reported in 1957 A little less than a third had no organic disease, a little less than a third had severe hypertension, and the rest had a wide variety of painful, disabling, or fear-engendering diseases It is, of course, impossible to assess in each case how far the physical disease contributed to the suicide What is clear is that the suicides encountered in the Keighley district have been, on the whole, a group of unfit or seriously ill people

I am indebted to Mr Stephen E Brown, H.M Coroner for the Craven District of Yorkshire, for permission to publish details of these cases, and to Prof Erwin Stengel and Dr Maria Pfister for their interest and advice.

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MEDICAL PROTECTION SOCIETY

Sir Ernest Rock Carling was president of this society for sixteen years and was in its office, going through the annual report, on the day before his death In his address to the annual general meeting on Oct 5, Dr E **Harwood Stevenson**, the chairman of council, spoke of the efficiency, the kindness, and the character Sir Ernest brought to the society's work.

The society has found permanent quarters at 50, Hallam Street, London, W 1, formerly the house of the General Dental Council On Dec 31 the membership stood at 35,551 and the financial reserves at £273,157, and the year's income of £96,575 exceeded expenditure by £22,869 In his financial report, the treasurer, Mr W M Mollison, points out that this surplus must be considered exceptional, and that " during the past year many serious cases have been undertaken on behalf of members and these could eventually involve the payment of substantial sums ", but " there is not ", he told the meeting, " the slightest reason why we should increase our annual subscription-rate of £2 "

Dr Stevenson said that things which get doctors or dentists into difficulties often do so not because of the thing itself but because of the way it is handled For instance, thiopentone leaks after injection give rise to complaint either because they are not recognised, or not dealt with, or because the patient is not given adequate information about what has happened Radial-nerve palsy from injections in the upper arm can also cause difficulty, and nowadays there is the risk of sepsis following hydrocortisone injections, " presumably due to the lowering of local resistance to even the smallest dose of bacterial contamination ", Difficulties can be avoided (1) by recognising the possibilities, (2) by guarding against them, (3) by recognising something wrong as soon as is feasible, and (4) by doing something properly about it The keeping of good records counts in all these things

Another illustration is the fractured jaw in dentistry, which is now clearly recognised by the courts as not in any way presupposing negligence on the part of the dentist. The questions which arise are whether there was adequate examination beforehand, recognition of the accident, arrangements for treatment at the earliest possible moment, and a plain statement to the patient. " The same pattern runs throughout so many of these instances If they are recognised, dealt with, and stated, the necessary protection is almost unnecessary as the thing protects itself "

Dr Stevenson also referred to the importance of a case which drew from the Judicial Committee of the Privy Council " not so much a definition of misconduct in the professional respect but certainly a definition of certain aspects of what may be alleged to be infamous conduct in the profession " The Society's annual report quotes Lord Jenkins as saying that " to make such a charge good there must be in their Lordships' opinion (generally speaking) some element of moral turpitude or fraud or dishonesty in the conduct complained of or of such persistent and reckless disregard of the dentist's duty in regard to records as can be said to amount to dishonesty for this purpose "

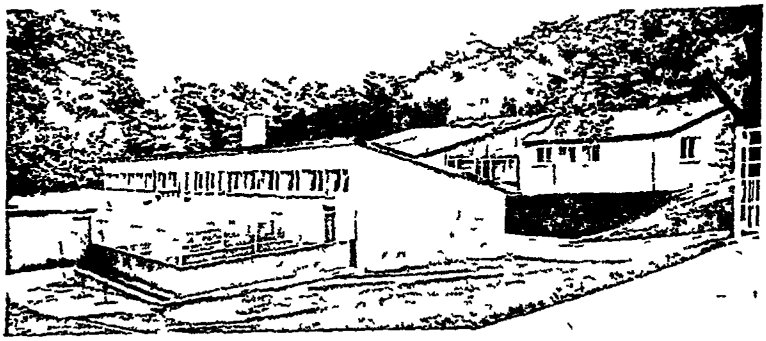
Mr W M Mollison was re-elected treasurer and Dr Alistair French secretary The appointment of a new president is under the council's consideration

NEW SURGICAL RESEARCH LABORATORY IN GLASGOW

On Oct 4 the Wellcome Research Laboratory, University of Glasgow, was formally inaugurated by Sir Henry Dale, who praised particularly the facilities created for joint research by investigators in human and veterinary medicine possibly for the first time, on a deliberately organised basis, in this country He recalled the valuable results of earlier exercises in " reciprocal fertilisation of ideas " in the early days of virology, when teams working on projects sponsored by the National Institute for Medical Research and later the Medical Research Council, almost fortuitously using the ferret as host animal, isolated the virus of canine distemper and then that of human influenza

The laboratory was built and largely equipped from funds provided by the Wellcome Trust, in order to provide first-class facilities for research in human and in veterinary medicine

The building is situated in the Garscube estate, reasonably close to the new animal hospital and laboratories of the veterinary division of the faculty of medicine It is a single-storey structure on three levels, planned with a view to economy on a steeply sloping site The construction is of the simplest form—load-bearing brick walls, metal roof decking with mineral felt finish, precast concrete floors The external design harmonises with the existing Veterinary Hospital buildings and with the surrounding woods and parkland. The internal surfaces are mainly painted plaster with linoleum and red asphalt floor finishes The laboratories, which are heated by hot-water floor panels, are very fully equipped with all services including oxygen, anæsthetic gases, compressed air, and a vacuum exhaust system



The working area of the unit contains two spacious operating-theatres and three laboratories One of the operating-theatres is of normal orthodox construction, the other has been screened to permit of precise electronic observations and recording without interference The three laboratories form a unit of two work rooms with a biochemical laboratory between, separated only by benching and glass screening This area was designed to facilitate multiple continuous observations on gastrointestinal physiology The kennels are in two separate blocks —a quarantine reception block and a " clean " block.

At the time of its official inauguration, the laboratory had been in use for several months and its resources were already fairly fully committed to research projects—some under the ægis of the two departments of human surgery and several organised jointly between these departments and those of the School of Veterinary Medicine The facilities of the laboratory will be available not only to members of the university departments, both clinical and preclinical, but also to the clinicians of non-professorial units The buildings and the site will lend themselves to extension

Photograph by Mr A. Finnie, of the University of Glasgow Veterinary Hospital and School.

The Widdicombe File

LXIV.—A DIVISION OF PATHOLOGISTS

DEAR IAN,

It should soon be all over bar the doing The ten years' shouting, always loud, sometimes bitter, over the projected College of Pathologists is to come to a head at last. The ballot papers for the crucial and we all hope final ballot are now printing, and within the month (saving a possible Path. Soc. postscript in January) the die should be cast at last.

It will, I suspect, be a near thing But not in the least in the direction that seemed likely in August, 1959, when I last wrote to you.[*] Then we had a majority committed to a College, but also a strong and vociferous minority which seemed determined to oppose it to the last ditch. Now the Physicians have intervened, and the pattern has changed. The do-nothing dissidents have all but vanished, and action is the cry on all sides But there are now two possible forms of action to go ahead with an independent College as originally planned, or to join the College of Physicians as a Faculty (or perhaps, since the status of the College of Surgeons' Faculties has made this something of a term of abuse among pathologists, a Division)

We had a lively and revealing debate at the recent general meeting of the Association of Clinical Pathologists, which, as you know, has been chiefly handling this matter on the pathological side It was made very clear that the council of the A C P and many of the older and wiser heads have firmly decided for the Faculty Most of the speeches from the floor, however, spoke hotly for the college. Apart from a most statesmanlike presidential address,[†] the council handled its case badly, I thought, and much of the attack on it was the irresponsible agin-the-government kind that rears up in any society when its executive seems too obviously to be imposing its own policy, however good, but some of it was genuine enough A ballot at the meeting would certainly have given a substantial majority for a College, but the bulk of the society's members, who have not much time to spare for annual general meetings in London, may have other opinions There is the Pathological Society electorate to consider also

Let me rehearse the main arguments on the two sides Make what allowance you like for my own preference for the faculty I think I am being reasonably fair Accept if you will also that the two main *practical* objects (i e, apart from flag-flying) of any such organisation are to act as a high-level negotiating body for pathologists, and to provide an examination structure of equal standing to that existing in most other groups of consultant medicine

For the independent College, it is agreed that we are the fourth largest body of consultants, much larger than the Obstetricians and Gynæcologists, who already have a College [‡] We stand for the scientific basis of medicine, related uniquely and fundamentally to every other branch of medicine, certainly not to be subordinated to, and hardly properly to be joined even on equal terms to, any other one of these branches If we become our own masters, we may do what we will if we join the Physicians, we must dance at least in part to their tune The Physicians would have none of us till it was unmistakably demonstrated that we were resolved to go it alone now they seem eager to prevent our setting up a rival establishment However fair the terms of the joining may be, the Physicians' persisting majority on the Comitia (not in the past a notably broadminded or progressive institution) could be used to ensure we do nothing to displease them *Timemus Danaos*, and the Physicians (it is said) are notable Greek scholars

The arguments on the other side have in contrast a distinctly sober-sided look. Financially, an independent College would be a cripplingly expensive undertaking, and though it would probably be able to count on some benefactions once established, for the first stages we would have to pay our own way—and we are neither rich ourselves (though Pilkington assures us we have almost our share of the Awards) nor as often as the clinician are we the friends of the rich At best it would be years before such a College had sufficient stature to be accepted as a proper negotiating body (remember that at present to the Minister the College of Physicians is our official mouthpiece) Its examinations, however good, would be equally long in acquiring the status they would gain at once if the R C P guaranteed them as equivalent to its own Membership If we committed ourselves to an independent College, and it failed (as, from mismanagement, dissension, or bankruptcy it *could* fail, though it should not), we would be terribly the worse for it if after an honest trial of union with the Physicians we found ourselves unable to agree with them, nothing could stop the faculty then splitting off and going its own way, with all the advantages of experience and an established organisation to help and nothing lost but a little time The argument that it is absurd for a pathologist to call himself a Physician will not hold water a third of the Physicians already are non-physicians in the narrow sense, and the title Physician, in the days when the College acquired its name, meant simply a reputable medical man with a degree. And finally, as I have argued before, there are too many Colleges already, and we, who count ourselves a unifying force in medicine, should not bear the reproach of starting yet another splinter group

If we were all certain that we could trust the Physicians, I think few would hesitate to accept their offer For it is a most generous one Its crux is the eligibility of holders of the pathological Memberships for the Fellowship (the straight F R C P) on the same terms as existing Members No existing faculty approaches this equality of status

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[*] We published this letter (*Lancet*, 1959, ii, 231)

[†] See *Lancet*, Oct. 15, 1960, p 863

[‡] The Pilkington report gives the following figures for 1958 1002 general surgeons, 952 general physicians, 855 anæsthetists, 744 pathologists, 704 psychiatrists, 507 radiologists, and 504 obstetricians and gynæcologists of smaller specialised groups such as neurosurgeons and pædiatricians, 928 in all probably count as surgeons and 719 as physicians

Why do people still not trust the College? It is in many respects the most reputable *medical body in the country* It suffers still, however, from having spoken in the past too often for itself and its fellows, when it was called on to speak for the whole profession It is still "of London" when it ought to be "of England" at least sometimes it has seemed to be "of Harley Street" (Of 24 men on its council, 19 are Londoners and a majority in private practice there) Its Comitia is a medieval or even primitive Greek oligarchy Members have hardly more rights than helots It needs a good deal of reforming But the wind of change is blowing there as elsewhere, if only because the centres of power even in consultant medicine have shifted greatly since the N H S began This offer to the pathologists is one which we can safely prophesy is only the first outward sign of a change of heart May it prosper!

Whatever the result, let us hope that there will be an *end of bickering*, a joint effort to make one or the other scheme work We are not like the Labour Party, choosing between two profound evils our choice is between two goods, and the greatest risk is that, like Buridan's ass, we may perish of indecision between them

May we hope then, Ian, for your good wishes that we may choose wisely, and, having chosen, proceed to action without more argument but may I hope also that you will, like me, cheer just that little bit louder if the soberer counsel of the Faculty party prevails?

Yours,
PETER DAVEY

Conferences

SEXUAL DEVIATION

FROM A CORRESPONDENT

A USEFUL conference, sponsored by the Portman Clinic, on the pathology and treatment of sexual deviation, was held in London on Oct 11 and 12

Opening the proceedings, Mr **KENNETH ROBINSON**, M P, described some of the difficulties he had faced in attempting to pass the Wolfenden proposals on homosexuality through the House of Commons Though the Press and Church had been generally in favour of change, and surveys of public opinion had suggested that nearly 50% of the population were ready for it, Parliament had divided two to one against Opposition had been irrational or deeply prejudiced Just as in the last century when select committees on lunacy had been years ahead of their Governments so, he was sure, the Wolfenden recommendations would eventually be passed He found it hard to see why, with our otherwise liberal traditions, we should have more repressive and illiberal laws on this subject than in any other civilised country

A General View

Speaking as a general psychiatrist, Dr **DAVID STAFFORD-CLARK** outlined the ethical problems of treating, often at the instigation of the wife, patients who did not really want to change or who wanted to change too much, by some mutilating sex-reversing operation Such procedures, he emphasised, should never be permitted, save to complete imperfect development, as in true hermaphrodites Wives sometimes asked psychiatrists to alter the husband's sexual practices without his knowledge! But even were this conceivable—by some form of tasteless drug—could a doctor rightly treat any patient without his willing cooperation? He also counselled against doctors advising marriage, divorce, pregnancy, or abortion On homosexuality, he noted that prejudices were as deep in our profession as elsewhere, and some clearly talked of "treatment" as a euphemism for punishment

Unlike most later speakers, Dr Stafford-Clark was impressed by the evidence of a genetic/constitutional basis in many cases, though most of the 40% or so of men who had at some time experienced a homosexual orgasm should be regarded as "normal" Seduction of the young, he was sure, played little or no part in the genesis of homosexuality, undesirable though it might be Conditioning as a form of treatment he found unsatisfactory practice was less clear-cut than theory and the time spent was often as great as that in psychotherapy Furthermore, with such deeply-laid disorders, he could not approve a treatment which dealt mechanically with one small aspect of behaviour to the neglect of the whole person A compassionate interest was needed, with respect for the individual, and psychotherapy was always valuable

In an unusually lucid review of the evolution of psychoanalytic thinking, Dr W H **GILLESPIE** pointed out that the diagnosis, "perversion", referred to behaviour that was habitual and which interfered with the biological function of sex—not to an occasional indulgence or fantasy Perverted sexual behaviour represented a persistence of infantile sexuality into adult life, the variety depending on the erotic stage at which the subject had become fixed This persistence, blocking normal adult genitality, served to ward off œdipal anxieties and, in genesis, was not unlike the neuroses—described memorably by Freud as "the negative of perversions" The preoccupation in fetishism with a non-genital area or some article, usually of clothing, represented intense castration fears that made it impossible for the boy to accept the reality of the female genitals He denied to himself that the female *can have no phallus* and constructed one out of the fetish object

Animal Behaviour

An ethological view of sexuality was put by Prof N **TINBERGEN**, who discussed some ways in which animal mating behaviour might shed light on the sexual instinct His film of a colony of black-headed gulls showed how "escape" and "attack" behaviour during the early territorial squabbles carried over into mating where it "released" sexual responses instead of combative ones These components of "attack" and "escape" behaviour in animal mating provide a biological basis for ambivalence It seemed to be the presence of "appeasement" postures which, in pair formation, allowed sexual to dominate hostile behaviour This aggressive component in sexuality may be an evolutionary "hang-over", and its occurrence in species which defend territories suggested its origin Territory defence here was clearly of survival value to these species He had noted males mounting other males at times of great sexual frustration (at the end of the season) and where a crouching posture of one had "released" this behaviour in the other, but the assaulted male at once repelled the onslaught Only once, in a female kittiwake, had he seen incomplete sexual behaviour, although with captivity and under-nourishment sexual deviation was often seen

Treatment of the Homosexual

Discussing the treatment of the male homosexual, Dr W **PATERSON BROWN** did not share the view that nothing much could be done in care and comfort—a disruptive approach, he thought, leading to poor results Help could always be given and cure should not be ruled out While homosexuals were often afraid of losing the only form of sexual expression they had, in fact one was adding something and aiding development The key he saw in the general character of the homosexual, a perpetual adolescent afraid of the more challenging aspects of everyday life, and living below his intelligence and potential Dr D J WEST, however, in discussion, believed there was good evidence that many homosexuals were well adjusted, living useful lives and never coming to psychiatric attention Their personalities, apart from this encapsulated disturbance, were normal Many matured naturally to heterosexual life

Desire, continued Dr Paterson Brown, was most frequently for the good-looking intelligent boy to which the homosexual wished to return, or for the large hairy masculine man, in working clothes, the homosexual trying thereby to incorporate the father-image and overcome castration fear Strong passive tendencies were usual, and fetishist elements often coexisted. Sexual fear of women extended to other spheres apart from the relationship with mother which was characteristically strong and ambivalent. The obvious truth that woman was the normal companion of man would be vehemently denied. The origins of homosexuality lay in wounding events damaging the developing ego in the male role—such as adoption, illegitimacy, illness and operations, deformity, a dominating smothering mother (especially common), a weak easily dominated father providing a poor role-object, and divorced or quarrelling parents ambivalent to marriage and the child Spoiling, asking too little, and giving too much also retarded development.

Treatment was most rewarding in the younger person of high I Q without serious defect in health or in social and educational life. Success depended on the quality of the therapeutic relationship plus the skill in interpretation, present acts had to be viewed in the light of what had gone before Injudicious bombardment with textbook interpretations was harmful and could lead to dangerous acting-out Attention was called in the discussion to disinhibited " psychopathic " persons, especially in prison, who seemed able to practise any form of sexual activity with anyone The most obvious homosexuals sometimes proved to be even more active in heterosexual behaviour Dr STAFFORD-CLARK pointed to the inadequacy of present therapeutic services One case he referred to the Institute of Psychoanalysis had waited five years after the initial interview before he gave up waiting Despite such demand, however, it was still possible for some to doubt the efficacy of analytical treatment and to ascribe recovery to the process of maturation

The Indecent Exposer

Dr ISMOND ROSEN said that exhibitionism was exposure of the genitals to someone of the opposite sex Though normal under 5, and as a prelude to intercourse, when it is practised outside the sexual act or as the major source of sexual pleasure it becomes a perversion Numerically such men are common representing a quarter to a third of sexual offenders, with a good number of offences unknown to the police. Of 490 offenders in 1954, only a quarter were referred by the courts for a medical report The 20% of indecent exposers who repeat their offences form the largest recidivist group of all sex offenders and are among the hardest to treat Dr Rosen based his observations on 19 cases treated in three separate weekly therapeutic groups and 10 who had individual psychotherapy He distinguished two varieties the simple or regressive type where the act followed some rather obvious social or sexual trauma, physical or mental illness, old age, alcoholism, or bereavement Such people were usually shy, inhibited, and fearful, but their personalities and work records were on the whole good and in other spheres they were highly moral The second type, the phobic-impulsive, tended to recidivate and were more often amoral, with other perversions and stealing They were shiftless and irresolute and often had phobic disorders, either hysterical or obsessional

The setting of the act was highly significant in arousal the time, the place, and the person to whom the behaviour was directed, all reflected dynamic internal events and the act was often repeated under identical circumstances, such offenders were readily caught the more so because their guilt was great All these details must be worked through in therapy Other cases seemed to respond more to internal sexual excitement Œstrogens suppressed the libido for a time but, as other speakers agreed, left the basic condition untouched, and breast development and other changes might bring greater disability than exhibitionism. Though there was inability to control the immediate impulse, the condition was unlike a compulsive neurosis where acts were accompanied by anxiety rather than pleasure Scoptophilia (voyeurism) was the counterpart of exhibitionism as sadism is of masochism or masculinity of femininity Exposure to a stranger was in part an aggressive act, representing an assertion of masculinity—a defence against castration anxiety—but intercourse in this context was usually the last thing such men wanted or were capable of They often married but were prudish with their wives, and their passivity was such that constant pressure by letter or by the probation officer was needed to ensure regular attendance for treatment As to results, of the 14 adult patients who were of the phobic-impulsive type, 13 appeared to have stopped exposing themselves, though 6 still had urges which they could control There was clear personality improvement in 6 and slight improvement in 5 Of the 5 adolescents who attended regularly, 2 went to approved schools for different offences, but 3 did well

The Sexual Murder

Drawing on his work in Wormwood Scrubs, Dr A HYATT WILLIAMS described the psychopathology and treatment of some sexual murderers, perhaps the most socially important variety of murder owing to its repetitive character The sexual murderer was but dimly aware, if at all of his motivation and it was clear that certain situations, with a type of victim who represented a key figure in a forgotten episode, could " trigger off " an uncontrollable and superficially incomprehensible assault The recurrence of the situation had the same effect Many people, doubtless, carried such potentialities but never encountered the trigger situation This catathymic crisis, as it had been called, often represented the explosive projection of a carefully cordoned-off area within the unconscious of an apparently sane person, securing a return to intrapsychic equilibrium. The bizarre clinical features of 5 cases described by Dr Williams—even excluding unconscious phenomena—scarcely admitted other than a psychoanalytic interpretation

In discussion he agreed that while violent or sexual offences often recurred, there was so far no way of picking out the potential killer from the mass of offenders The cultural pattern of murder differed for example, in the U S A where murder was vastly more common, the precipitation of such acts was much more trivial, and suicide afterwards less common than here. Psychotherapy must necessarily take place in a prison setting, the patient even realised this and was grateful for the security against acting out, psychotic withdrawal was a further risk.

Role of " Aggression "

In a detailed account of aggression in the ætiology of sexual deviation, Dr EDWARD GLOVER tried, in this eclectic but rather Freudian-weighted conference, to find a common ground for understanding Psychoanalytic concepts of the unconscious were working hypotheses throwing light on clinical manifestations, and they might, he said, have some therapeutic applications Basically, he postulated two drives or instincts, those of sex and of aggression, destruction, and mastery He preferred to think of constitutional predisposing (endopsychic) and precipitating factors (immediate or summating) where outcome depended on the innate strength of both drives plus the degree to which these two became fixed at certain stages in development. It would be absurd to reduce ætiology to a one-factor system—that of aggression—though its role in mental function was very wide indeed On this his views were substantially those of 30 years ago

Sex and Culture

Describing some cultural differences in sexual deviation, Dr G M CARSTAIRS showed that "normality" needed to be judged in its environmental context Different cultures gave the stamp of approval to quite limited aspects of human sexual behaviour, while restricting others, often with great severity Though Western cultures showed great variations—between Scandinavia, say, and Spain or Sicily—the "popular" British culture remains a restricted one, viewed internationally Differences were noted in attitude to premarital behaviour and to marriage itself, in the outcome of which society had so much at stake—symbolised by the ritual surrounding until recently our own Royal marriages and the consummation thereof

To break the taboos on marriage was usually held to bring harmful consequences on the whole community, whereas neglect of extramarital prohibitions brought them upon the individual in the form of an illness or public disgrace Incest taboos differed—*e g, in the Trobriand Islands where an* injunction to copulate with the mother might seem jocular, with the sister insulting, and with the wife an occasion for duel to the death Polyandry or the offering of a wife to an honoured guest—as the Eskimos did—seemed especially bizarre to us Most tropical societies permitted far greater sexual freedom to children and adolescents, even encouraging early intercourse "Decent" clothing varied greatly to a Trobriander male it involved only a palm-leaf and to the Uruba of Brazil merely a string round the prepuce Shame and odium were equal should either slip—a commentary on our views on exhibitionism It was the deliberate flaunting of custom rather than the nakedness which constituted indecent exposure

Quoting the classic work of Ford and Beach, Dr Carstairs illustrated how the range of love-play increased with ascent in the evolutionary scale, as did the need for training and practice on the part of the male This was especially true of humans, and there were strong grounds for believing that adolescent inhibitions, as we tend to encourage them, can be a serious handicap in attempts to achieve satisfactory relationship in marriage The sex-inhibited Hindu community, for example, flowed over with fears of impotence (the third commonest complaint in Dr Carstairs' village clinic) whereas the tolerant and romantic Bhil tribe, nearby, showed almost none

Less evidence existed regarding deviant practice but it should be noted that the infliction of pain was commonly "normal" (by the male on the female in animals, but mutually in human tribes), and "battle-scars" of sexual encounter were sometimes cherished Homosexuality was world-wide in incidence and 49 out of 76 well-documented societies thought it normal or desirable under certain circumstances Only in 28 (including our own) was homosexuality proscribed That such behaviour seemed very rare in the uninhibited culture of the *Trobriand Islands went against the constitutional/genetic* theory, as did recent studies of hermaphrodites which showed how sexual orientation was determined by the role assigned by the parents and not by chromosomal, gonadal, or hormonal patterns

In the discussion, one view evoking much applause was that the new liberal outlook of most headmasters seemed to correlate with healthier and less neurotic student life There was a great need to throw out wrong ideas about sex from the educational system, notably concerning the alleged evil effects of masturbation

The organisers of the conference hope to publish the full proceedings later

Public Health

Public's Views on Health Education

Dr H D Chalke, medical officer of health for Camberwell, describes in his report for 1959 an attempt to assess the public's opinions on techniques of health education Over 600 copies of a questionary were completed 4% of the replies came from persons in group I (professional workers), 14% from group II (intermediate), 71% from group II (skilled), and 11% from groups IV and V (semiskilled and unskilled) Schoolchildren and senior students were grouped separately, and the replies were also broken down by age and sex

The first question asked for the following to be placed in order of importance as a means of health education (*a*) magazines such as *Family Doctor*, (*b*) newspaper articles, (*c*) pamphlets, (*d*) posters, (*e*) films, (*f*) exhibitions, (*g*) radio programmes, (*h*) television programmes, (*i*) visits to maternity and child-health centres, (*j*) talks at clubs, (*k*) talks at school

Television programmes were voted first by all categories except two schoolchildren favoured films and television equally, while men over 60 gave first preference to newspaper articles The professional and intermediate workers gave newspapers, the radio, and posters as their next three choices, skilled workers the radio, newspapers, and talks at school, semiskilled workers radio, posters, and newspapers, and unskilled workers, films, magazines such as *Family Doctor*, and posters

Senior students chose talks at school, newspaper articles, and the radio, and schoolchildren placed films second, magazines third, and talks at school fourth

Exhibitions, which are costly to arrange, came low on the list, and so did pamphlets and talks at clubs The value of visits to maternity and child-welfare centres was stressed only by those actually attending them

74% were in favour of more money being spent on health education and only 13% against More health instruction by means of talks and films was advocated for schools and for scout and youth organisations, particularly by those in the 26–35 age-group Films on health subjects were suggested and newspapers and magazines, mobile health exhibitions and radio programmes proposed as possible means of health education Fully a quarter of those in favour of increased expenditure considered that the additional money would be best used on television programmes In this connection documentary films and Government advertising on commercial television received special mention

Vital Statistics

In his latest quarterly return[1] the Registrar-General includes a report of the work from 1957 to 1959 of the Advisory Committee on Medical Nomenclature and Statistics A small inquiry comparing the diagnoses entered on medical certificates of cause of death by clinicians before necropsy and by pathologists after necropsy revealed that in about a fifth of the cases a new finding was recorded as a result of the necropsy A larger inquiry was carried out over six months in 1959 in 100 hospitals, and the results are being analysed

The committee urges that the cancer registration scheme should cover the whole country At present probably about 70% of new cancer cases are being registered.

The return gives provisional figures of causes of *death in* 1959 by sex and age The total of 66 deaths attributed to acute poliomyelitis is the lowest since records were begun *in* 1911 The low number of 25 deaths from whooping-cough also represents a record Deaths from measles (98), on the other hand, were double the 1958 total, but the same as in 1957 Figures for cancer of the lung (21,063 [18,181 men and 2882 women]) showed an increase of 1243 over 1958 throughout all age-groups except the youngest and women aged 25–44

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[1] Registrar-General's Quarterly Return for England and Wales, *no* 446 H M Stationery Office Pp 28 *2s*

In England Now

A Running Commentary by Peripatetic Correspondents

RECENTLY we formed a Supporters' Association. This is of course, to be distinguished from the hospital's League of Friends, which exists essentially to do good. The Supporters' Association is frankly for the benefit of its members It arose in this way

We long ago observed that a considerable number of patients attended the hospital but evidently did not wish to see the doctor, since they paid little attention to the advice given or treatment recommended. Did they (we wondered) come to see the nurses, to enjoy one another's company or just to enjoy the general hospital scene? Careful research showed that all three elements played a part. We found that when we put all the attractive nurses in the casualty department the number of young men with sprained ankles, foreign bodies in eyes wax in the ear, &c., reached astronomical proportions We observed that certain patients came in groups if Mrs B came then Mrs C would come also, and so on. A third section of patients apparently came to enjoy the hospital scene—to witness the little contests between patient and doctor or sister and house-surgeon.

It was clear, therefore, that if the Supporters' Association was to be a success it must provide all three types of amusement and adequate variety, and the results of doing so have exceeded all expectation. Though the number of hospital attendances trebled in two years the numbers of outpatient consultations, minor operations, X-ray examinations, and pathological examinations have all fallen to about a quarter

Moreover we have the extension to our outpatient department so often rejected by the regional board for lack of funds On the last occasion we reported their refusal to the secretary of the Supporters' Association who at once came to our rescue. On the day when a visit by an official from the Ministry of Health and our local Member of Parliament was arranged, the Supporters turned up in force and the scene resembled an Indian railway-station The visitors were visibly impressed and went away badly shaken. A few days later the treasurer of the regional board informed us that there had been a special capital allocation of £25,000

Some discussion arose on how this should be spent, for the Supporters very reasonably felt themselves entitled to a share. They suggested that a news-reel be provided in the outpatients, but in agreeing to this our committee stipulated that Supporters should not enjoy the outpatients' amenities and the news-reel and *also* visit the doctor or have an X-ray examination We felt it was our duty to protect our fellow taxpayers' pockets This was accepted and there was yet a further fall in the number of outpatient consultations—so much so that one or two physicians, becoming quite fearful for their jobs, have lately been giving free cups of tea with the consultation

On the whole we may justly claim that the system has been a success, and that we now provide a better public service. Students of social medicine should certainly visit our hospital and see this pioneer experiment.

* * *

For the princely sum of six shillings, readers of *The Lancet* (and less fortunate mortals too) can acquire a handsome paperback from the respectable presses of Her Majesty's Stationery Office,[1] whence, if they will rustle up their slide-rules, or leaf through their log books, they may place themselves securely in the Great Chain of Materialist Being, verify, if they will, the logarithmic law of income, or plot some pleasant percentile curves

Do you, Sir, a struggling registrar, cry nightly "God for Harry" (Pilkington of course)? Believe me truly, not more than 1 in 10 of our island population is your financial peer, and between you almost a third of the national cake is yours for the sharing Or are you older now, the grey hairs of senior registrardom lending distinction to your brow? For you too I have news not 1 in 20 of your fellows can boast a fatter wallet But alas, the going is harder now and the curve steeper, for you sit (little did you know it) an awkward saddle, at a discontinuity of slope. You guessed as much? Take heart even your supertaxed and learned seniors have almost half a million men to keep them company

* * *

Well, we've certainly got ourselves on the map though we were almost washed off it in the process Our little seaside town had just said goodbye to its summer visitors and was slowly preparing for hibernation when the rains came. It rained for a week and hundreds of houses were flooded, and then it really rained. We became top priority in the news, and our little brook won world fame. The streets were filled with little boats bringing food, water, and firewood to well over a thousand marooned in their upstair rooms The Army helped, the Marines helped, and the voluntary organisations worked wonders Water was pumped out of houses Money was poured into a relief fund and the floods subsided. Now there is only the mopping-up left.

What has all this taught us? Where are the pneumonias and chills so gloomily predicted? Surgeries and visiting lists are no longer or shorter than usual The people of the West Country are tough and that it takes more than a big splash to knock them off their feet.

* * *

Every October worried parents bring their eleven-year-olds to the surgery He, or she, is off colour, won't eat, can't sleep, or has begun wetting the bed again. Full examination and reassurance satisfies the doctor, but the mother wants a diagnosis "It is the 11—," I tell them. Monthly observation is offered—if it wasn't I should get a weekly emergency call for each new symptom. As E-day approaches tension mounts, diarrhoea and vomiting alternate with constipation and frequency Then comes the report of the trial I have to listen patiently to a question-by-answer commentary of the ordeal undergone. Four months of relative quiet ensue. The examination papers mature in some council office. By June they are ripe and the verdict is given. The education officer allocates the place in the new school Johnny is going to the grammar school, Mary to the secondary modern, Willie to the technical school, and Frances has got one of the two places at the girls' public school

Sometimes I am surprised at the outcome. Occasionally the parents are mystified Herbert, who has been as regular an attender for the past nine months as an expectant mother, came to see me last week with Mrs Brown, who told me "He's going to one of them new contraceptive schools, doctor"

* * *

First it's cells, now it's tissues, and soon whole organs will be refrigerated into indefinitely suspended animation, said our consultant optimist. Banks for blood, banks for marrow and bone and arteries—simply a matter of time and we shall all enjoy a comprehensive service for reliable spare parts The next step will be to store the body complete and thaw it out when we feel that the time is ripe to return it to physiological and social circulation. We shall then be able to stockpile our existing geniuses for future scarcity or the edification of generations to come. Take the virtuoso musician off the ice in A.D 3000 long enough for them to hear his Bach, and then pop him back into cold-storage for another century or so Let us deep-freeze Lord X, Sir Y, and Mr Z and bring them out as a coalition or individually (depending on the political preferences of the time) when England is in peril. One refrigerator should serve for all three, it will be quite economical Only take care to label the body correctly, and posterity will do the rest

Deuced awkward for posterity, observed our consultant pessimist, if there's a longish power-cut.

* * *

Overheard in the ward—"This patient's son is to be married next week. Can she have compassionate leave to go to the wedding?

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[1] National Income and Expenditure, 1960

Letters to the Editor

MOTOR-CYCLE ACCIDENTS

SIR,—All surgeons responsible for the immediate treatment of major injuries to motor-cyclists will welcome Dr Bothwell's article of Oct 8 In spite of considerable recent advances in resuscitation, diagnosis, and early treatment far too many of these injuries are beyond the possibilities of complete surgical repair and in some it is not even possible to save life The most important part of the medical attack on this aspect of road-accident problems must be in the prevention of injuries or the lessening of their severity

Many surgeons, against the background of their experience, would advocate the abolition of two-wheeled vehicles from our overcrowded roads To some extent this is already happening in the United States and will occur in time in this country In the meantime the approach outlined in Dr Bothwell's article demands urgent and serious consideration

Our recent studies of the causes of severe injuries to motor-cyclists underline the importance of two causative factors A large number of irreparable and often fatal cerebral injuries result from the rider's ejection off his bike after its front wheel has made glancing contact with a heavier vehicle as he endeavours to overtake it through a narrow opening After ejection his head may hit the road, make violent impact against another vehicle or road structure, or he may be run over His bike is often undamaged On this evidence crash helmets should be compulsory and some means of holding the rider on his bike is clearly a matter for urgent research study

Yet one wonders if roll and crash bars that increase the bulk of the bike would not be responsible for more glancing contacts with heavier vehicles in the congested road conditions that must remain for some time As Dr Bothwell states " We cannot legislate out the masculine propensity for speed " Neither can we " legislate out " the motor-cyclists' desire to overtake other road vehicles at speed even when the available space is minimal

Other increasingly common types of motor-cycle injuries are fracture-dislocations of the hip, or, if the hip withstands the force, grossly smashed and displaced fractures of the femoral neck or shaft, and, on rarer occasions, a combination of both These injuries may also be associated with sciatic-nerve damage and result in permanent deformities in spite of the most expert treatment According to our studies, such injuries are due to direct impact violence against a heavier vehicle while the motor-cyclist remains on his bike These injuries are considerably less frequent than head injuries It is extremely doubtful that safety harness even combined with roll and crash bars would prevent such crippling injuries

Although in agreement with everything that Dr Bothwell's excellent article advocates, I am in favour of special tracks for two-wheeled vehicles to be included in the design of new roads and so eliminate the possibility of the motor-cyclist's contact with much heavier road vehicles

WILLIAM GISSANE
Director, Road Injuries Research Group,
Birmingham Accident Hospital

COSTS IN THE HEALTH SERVICE

SIR,—Dr Ross (Oct 8) will find that on p 697 (col 1, lines 14–42) in my article of Sept 24 I discuss the way variations in use may be said to cause variations in the cost of hospitals My comments, with alterations in detail, would apply equally to a midwifery or ambulance service

Dr Ross's letter raises the practical problems of planning new facilities, and of forecasting fund requirements, at the level of a local authority, or an individual industrial firm They can be illustrated by the example of a town ambulance service at the beginning of the late war

Let us assume firstly, that the peace-time service can carry x patients in unit time when working at capacity, and secondly, that it is decided the carrying capacity should be doubled to meet expected war-time use What effect may this planning decision have on the cost of the ambulance service?

It may have none It may be impossible to obtain the extra vehicles, and the additional personnel required may not be available, or the request for more funds may be refused

On the other hand, the number of the vehicles and staff may be doubled, thus nearly doubling the cost of the service But these costs are nearly all fixed (overheads) and the rise in expenditure will occur, *whether or not the predicted rise in use actually takes place* If use of the service remains at peace-time levels, costs will continue at war-time rates If, however, an air-raid results in the need for $2x$ patients to be carried, or even $100x$ patients, there is virtually no increase in its cost

When making plans any organisation, working within the framework of the national economy, must attempt, as Dr Ross indicates, to forecast future use and the cost of providing facilities By the nature of the problem, events may often prove the forecasts to be erroneous, as suggested by the case of the ambulance service Furthermore, major errors in planning are not confined to the public sector of the economy When the American Ford Motor Company introduced in 1957 its new car, the Edsel, it anticipated sales of about 400,000 annually, and invested in the required installations In the event, only 100,000 cars were sold after two years, when, to stop further losses, it discontinued production The cost of research, design, tooling, and expansion of production facilities was 250 million dollars, most of which was a total loss to the company

When planning, at the national level, the total sum a whole nation is to spend on a publicly financed health service, the problem is quite different Attempting to predict future use will give no answers of any practical value to those framing the national budget Instead, one must look at the national income, as I have previously indicated[1 2]

Richmond, Surrey J R SEALE

BRITISH STUDENT TUBERCULOSIS FOUNDATION

SIR,—I should like to bring to notice the appeal for money to run the British Student Tuberculosis Foundation

The Foundation was created ten years ago so that students with the disease could continue their studies while having treatment There are now two units—an English one at Pinewood Hospital in Berkshire, and a Scottish one at Tor-na-dee near Aberdeen Over 400 students have passed through our units and an impressive array of examination results has been produced

Any student attending an institute of higher education in a full-time capacity is eligible for the unit, and of these one in

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[1] Seale, J R *Lancet*, 1959, ii, 555
[2] Seale, J R *ibid* 1960, i, 1399

every thousand will require treatment for tuberculosis each year This disease is no longer the scourge it once was but it is still common and serious and requires prolonged treatment

The Foundation needs £10,000 to pay for the cost of administration over the next few years—a small amount to ask in this day and age

Further information may be obtained from, and donations or covenants sent to, the Secretary/Administrator, British Student Tuberculosis Foundation, Pinewood Hospital, Wokingham, Berkshire

E J R ROSSITER
Chairman, British Student
Tuberculosis Foundation

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—I am writing in support of Dr Prior (Oct 8), who finds it difficult to accept that coronary disease in the younger age-groups is a different one from that in patients from 60 onwards Dr Prior also quotes Crawford, who, at the Royal College of Physicians symposium on occlusive heart-disease, stated that he found no evidence to support the view which is often expressed that fatal coronary disease in young men is a " different " condition from that in the more usual age-group

In my review[1] of 100 cases of coronary occlusion in young adults (under 35) who served in the second world war, in which the mortality was 80% and in which necropsies were performed, the pathological changes described in the coronary vessels, which in many cases were thickened, tortuous, and calcified, were similar to those found in the older age-groups A thrombus was found in only 22 of the 80 cases Occlusion in the non-thrombus cases took place as the result of the gross atheroma or of an atheromatous plaque blocking the lumen Atheroma of the aorta was also present in most cases

These findings do not support the view that fatal coronary disease in young men is a different condition from that in older men

Sanderstead, Surrey MAURICE NEWMAN

MANNERS MAKYTH MAN

SIR,—In the course of the last week I was interviewed with several others for a consultant post in one of the Metropolitan regions which now have their headquarters in a magnificent block of new buildings close to Paddington station

My letter of invitation to this interview was an untidy duplicated proforma measuring 9 in × 7 in on which the printing was barely legible The added typescript was badly aligned and ran obliquely across all the " blank " spaces my degrees were grotesquely misspelt and two significant mistakes in my address had been overtyped without any attempt at erasure The letter was not personally signed by the sender and as a final pièce de résistance the date at the top of the letter (stamped with a crude office stamp) was four days later than that stamped by the Post Office on the envelope in which I received the letter

I have seen better and neater orders typed near the front line in wartime, and in peacetime no secretary of repute would dare to send out circulars in such a state to members of his society or organisation

Most of us take very great care and sometimes spend a considerable sum of money in drafting and submitting our applications for consultant appointments Is it too much to expect some of the regional hospital boards to do the same?

SENIOR REGISTRAR

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[1] *Lancet*, 1951, i, 1045

ALL CYCLES ARE NOT MENSTRUAL

SIR,—May I try to put my point more clearly, since your comment of Oct 15, referring to Rogers' review[1] of a menstrual periodicity in various diseases, completely misses it? The facts first

(A) In men, though rarely, illnesses are seen where bouts of physical or psychiatric symptoms recur regularly at monthly intervals Some may recur more frequently than this, others less (anything from 2 to 60 days or more), but the interval is roughly constant for a given individual and may be around 30 days Perhaps I may add two references to those I gave before for this[2]

(B) In women, likewise, one sees cyclic illnesses recurring at fixed intervals Sometimes the interval is long (e g, 48 days), sometimes short (e g, 2 days), or has intermediate values, but it is roughly constant and characteristic for a given individual These illnesses continue after the menopause They follow a different rhythm independent of the menstrual cycle

These cases establish the point that there are regular rhythms of recurrence of symptoms which have nothing to do with ovarian, uterine, or gonadotrophin function, and are therefore not menstrual in origin There is some evidence that they arise through a malfunction in the central nervous system, and might be treated with phenothiazines or other neuroplegic drugs

Both (A) and (B) cases are rare There is however a large group of women who have illnesses recurring every 25–35 days, at about the menstrual interval The majority of these may well be a consequence of cyclic changes in œstrogen or progestogen level, for instance, which is what Rogers is discussing But it should be no surprise if some of them turn out to have quite a different pathology, independent of menstruation in spite of their monthly periodicity, so that they belong with the kind of cases described above under (A) and (B) with a possible C N S factor The case on which your leader of Oct 1 was based appears to fit in here[3]

The nature and location of the timing mechanism in the cyclic physical and mental illnesses of both sexes, showing weekly, monthly, or other regular periodicity of recurrence constant for the individual, is a matter for further research

All Saint's Hospital,
Birmingham J L CRAMMER

SIR,—Both Clarkson and his colleagues[3] and Dr Crammer (Oct 15) seem to have overlooked the part played by the pituitary in initiating the menstrual cycle, and they cannot understand why neither hysterectomy nor oophorectomy abolished the cyclical symptoms It would require a hypophysectomy to achieve this end The persistence of menstrual symptoms following hysterectomy and oophorectomy was the subject of a discussion at the Royal Society of Medicine in 1956[4] These cyclical symptoms appear to be related to a cyclical deficiency of progesterone, either directly due to deficient progesterone output from the corpus luteum or indirectly due to unbalanced stimulation from the pituitary, and alleviation of cyclical menstrual symptoms can be achieved by the use of intramuscular progesterone

Dr Crammer is confused by cyclical symptoms occurring up to six days before and three days after menstruation He rightly reminds us that before and after menstruation are different biochemical situations Confusion can also arise in some women in the numbering of the days of the menstrual cycle If a woman experiences slight spotting for three days followed by the full menstrual loss, which is the first day of her cycle? Premenstrual œdema and water retention are not relieved until the onset of the full menstrual flow, which in the example quoted would result in maximum symptoms on the third day followed by relief on the fourth day

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[1] Rogers, J *New Engl J Med* 1958, 259, 676

[2] Crammer, J L *Lancet*, 1957, ii, 259, *ibid* 1959, i, 1122

[3] Clarkson B, Thompson, D, Horwith, M, Luckey, E H *Amer J Med* 1960, 29, 193

[4] Dalton, K. *Proc R Soc Med* 1957, 50, 415

London, N 18 KATHARINA DALTON

STERILISATION OF RUBBER SHEETING

SIR,—I note with particular interest your comments concerning the near impossibility of sterilising rubber sheeting and I should like to make a suggestion

It is becoming clear that the major risks of infection lie in the hospitals themselves and I would be far happier using an expendable machine-made piece of sheeting rather than a sheet which is used again and again after contamination in the hospital, with problematical sterility I feel that the medical profession has overlooked the enormous advances in the production of expendable plastic sheeting I am convinced that in most cases where rubber sheeting is used really thin, cheap plastic sheeting (polyethylene or ‘ Cellophane ’) would be completely satisfactory for different purposes and cheap enough to throw away after use The thin polyethylene sheeting in particular has just as good a feel as rubber, and while it may not be obtainable truly sterile, it will not be contaminated with the resistant organisms which are causing the trouble in hospitals It is probable that it could be aseptically wrapped in the manufacturers’ premises and it would not be at all difficult to get it in rolls, which could be kept in a sealed container and drawn through a slot as required

Townson & Mercer Ltd ,
Croydon R BARRINGTON BROCK

SMOKING BY ADOLESCENTS

SIR,—Dr Edelston (Oct 8) tempts me to enter a discussion of some interesting questions, such as whether smoking is a moral delinquency, a vicious habit, or a pitiable addiction, whether it would be right or wrong to prohibit it by law, and whether a doctor can both smoke and disapprove of smoking

I should like to discuss any or all of these subjects, in my letter of Sept 24, however, I was trying to make some much simpler points about smoking I feel sure Dr Edelston can agree with them They are

(1) Adolescents who start smoking are likely to continue

(2) They are therefore in danger of lung cancer and chronic bronchitis

(3) Although we sometimes compel people not to do things which harm only themselves, we cannot compel people not to smoke because the majority think this would be an unjustifiable interference with their liberty

(4) No such consideration, however, applies to tobacco advertisers they are not trying to harm themselves, but other people They ought, therefore, to be prevented

It occurs to me now that it is just possible that this or some future Government might prohibit smoking by adolescents as a convenient way of “ doing something ” I think this would be a mistake because it would result in even more adolescents smoking even more cigarettes as a way of asserting their adulthood They would, of course, be enthusiastically encouraged by the advertisers “ Lucky Ron ! At last he’s 21, now he can *legally* enjoy the *manly* aroma of Blogg’s Benz Pyrene Cigarettes ”

I suggest that this kind of thing, deliberately intended to encourage children to harm themselves so that the advertiser may profit, has a very nasty name It would be practicable to prohibit it and the prohibition could be enforced If the Government hasn’t the necessary courage, it would at least be a start if the B M A could come out openly in favour of such a ban The smoking doctor could then honestly say “*I* smoke because I can’t help it, I advise *you not to start* ”

Halstead, Essex R E W FISHER

THROMBOSIS AND ANTICOAGULANT THERAPY

SIR,—Perhaps you will be kind enough to allow me to draw your readers’ attention to an error which appears in your account (Oct 15, p 870) of the symposium on thrombosis and anticoagulant therapy held recently in Dundee You quote me as having said that in a method for producing artificial thrombi “ the process was inhibited by short-chain fatty acids with upwards of 16 carbon atoms ” What I actually said was that the process was *accelerated* by *straight*-chain saturated fatty acids with 12 carbon atoms or more

A full account of these observations, which were carried out in collaboration with Dr William E Connor of Iowa, will be published in the *Quarterly Journal of Experimental Physiology* early next year Meanwhile I am sure that you will share my anxiety lest other workers in the field should be misled by the seriously inaccurate statement

Sir William Dunn School of Pathology,
Oxford J C F POOLE

TRUE HERMAPHRODITISM AND KLINEFELTER’S SYNDROME

SIR,—We were interested in the case of true lateral hermaphroditism reported by Dr Gordon and others (Oct 1), but are puzzled by the title of the paper, namely “ chromosome count in a hermaphrodite *with some features of Klinefelter’s syndrome* ”

It is obvious that in certain cases of true hermaphroditism the differential diagnosis of Klinefelter’s syndrome must be seriously considered when the patient is initially examined But even at the initial examination the diagnosis of Klinefelter’s syndrome must have been seriously in doubt in this case The invariable criterion of Klinefelter’s syndrome is micro-orchia—that is very small testicles, usually of firm consistency The testicles, however, are descended, and we know of no case in which Klinefelter’s syndrome has been associated with one undescended and impalpable testis Furthermore, in this case the one palpable testis was “ slightly smaller than would be expected for his degree of maturity ”

Hypospadias is very suggestive of hermaphroditism rather than of Klinefelter’s syndrome, in which condition it does not occur, in our experience If it did occur it surely would be regarded as a very rare chance association

Gynæcomastia occurs in cases of Klinefelter’s syndrome and may be marked, though the complete femininity of the breasts in this case should surely have aroused suspicion that this was at least atypical for a case of Klinefelter’s syndrome

The finding of a chromatin-positive buccal smear is, of course, suggestive of Klinefelter’s syndrome but equally suggestive of true hermaphroditism

A normal, rather than a markedly raised, urinary gonadotrophin excretion is another point against the diagnosis of Klinefelter’s syndrome The high level of urinary œstrogens is not typical of Klinefelter’s syndrome, though it might reasonably be expected in true hermaphroditism

Finally, the testicular histology is quite unlike that found in Klinefelter’s syndrome. In a patient whose secondary sex characters have already developed one would expect the classical picture of interstitial-cell hyperplasia associated with hyalinisation of seminiferous tubules with occasional Sertoli cells

We believe that the study of sex chromosomal anomalies is entering a phase in which it may be eventually possible to classify the anomaly in relation to the clinical picture It is therefore important, in our present state of knowledge, to be precise in our recording and diagnosis of those cases about which we have reasonable knowledge of the clinical condition In our opinion the case reported is a typical case of true hermaphroditism and does not show any of the classical features of Klinefelter's syndrome

P M F Bishop
P E Polani

Guy's Hospital,
London, S E.1

OBSTETRIC FLYING-SQUADS

Sir,—Mr Stabler (Oct 8) delightedly supports Dr Walden's suggestion that women can be as safely confined at home as in hospital Of course, but why stop here? We must all agree that obstetrics is the least predictable of all medical subjects, therefore, presumably it should be even more meritorious to have one's tonsils out on the kitchen table, as I did 45 years ago, and why not do all hernias, appendices, varicose veins, &c, there also? 28 years ago, I gave blood in a private house in Bracknell where the late Sir Thomas Dunhill assisted by Mr Paterson Ross (now Sir James) was doing a gastrectomy

Why not pull down all the hospitals and go back to the "good old days", or has the spirit of pioneering died?

London, W 1
Keith Vartan

ORAL HYPOGLYCÆMIC AGENTS

Sir,—We read with interest the letter of Sept 10 from Dr Locket and Dr Brown, because we have recently encountered two instances of coma in diabetic patients receiving chlorpropamide In both the coma proved to be due to hypoglycæmia, and we wish to draw attention to the possible effect of the usual therapeutic doses of the drug

Case 1—An obese alcoholic man of 55 was treated for diabetes of a year's known duration by a low-carbohydrate diet and a daily dose of 250 mg of chlorpropamide. His symptoms of diabetes were relieved, and when seen on five subsequent occasions the urine was sugar-free and the early afternoon blood-sugar varied between 85 and 115 mg per 100 ml. The day he was admitted to hospital, he left for work without breakfast. At midday he was brought home unsteady and aphasic. An hour later he became unconscious When admitted at 5 P.M. the same day he was in coma, and the plantar reflexes were extensor The blood-glucose level (auto-analyser) was 30 mg per 100 ml on admission and he rapidly regained consciousness after an intravenous injection of 40 ml of 50% glucose. Six hours later he became restless and mentally confused, but again rapidly improved following a further intravenous injection of 20 ml of 50% glucose. At this time his serum-chlorpropamide level was 8 5 mg per 100 ml (therapeutic range 2 5–17 5)

Case 2—A spare man of 62 was treated for mild diabetes of a month's known duration by 250 mg of chlorpropamide daily A month later, when his wife went to wake him, he was found in bed semiconscious and aphasic. He had been well the evening before, and had eaten his supper When seen at hospital he was semiconscious and had a right hemiparesis Since he was not known to be a diabetic, hypoglycæmia was not seriously considered. Blood for glucose estimation was taken at 10 A.M., however, and found to be 18 mg per 100 ml This reading was not known by us until 3 45 P.M., when his clinical condition was unchanged, and the blood-sugar at that time was 22 mg per 100 ml Given intravenous glucose, he quickly revived, but remained dysphasic for a further two days

Patient and relatives should be warned of the possibility of severe hypoglycæmic reactions to chlorpropamide Because of the prolonged action of chlorpropamide, the possibility of recurring hypoglycæmia should be kept in mind

J Bradley
M G FitzGerald
D J Scott

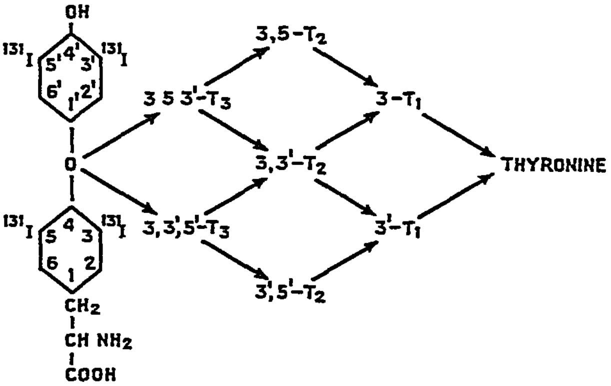
General Hospital,
Birmingham.

RADIOCHEMICAL SYNTHESIS OF TRIIODOTHYRONINE

Sir,—We have read with interest Dr Deutsch's (Sept 10) letter on the possible formation of ^{131}I-labelled triiodothyronine from ^{131}I-labelled thyroxine after the decay of one ^{131}I atom to ^{131}Xe We should like to make the following comments

In the work of Gross and Pitt-Rivers,[1–3] cited by Dr Deutsch, synthetic radioactive thyroxine, labelled in the 3′ and 5′ positions only, was not used Human subjects and experimental animals were given "carrier-free" Na^{131}I, which was converted to labelled hormones in their thyroid glands According to present concepts of thyroid hormone biosynthesis, iodide after entering the gland is first incorporated into the iodotyrosines, these are then converted by a coupling mechanism to thyroxine and to a lesser extent to 3,5,3′-triiodothyronine. The thyroxine thus formed from ^{131}I-labelled diiodotyrosine will be uniformly labelled, that is, all four iodine atoms in the thyronine molecule have an equal chance of being labelled

Now the decay of any one ^{131}I atom in the thyroxine molecule is not affected by its position, therefore the following products of decay should all be theoretically produced



Thyroxine would first yield the two isomers of triiodothyronine, 3,5,3′-T$_3$ and 3,3′5′-T$_3$ (the abbreviations used are those recommended by Harington et al [4]) These would give rise to the three isomeric diiodothyronines 3,5-T$_2$, 3,3′-T$_2$, and 3′,5′,-T$_2$ which in their turn would give the two monoiodothyronines 3-T$_1$ and 3′-T$_1$ Complete decay would finally give unlabelled thyronine.

In short time intervals after ^{131}I administration (1–24 hours) to animals, the thyroid gland would contain only minute amounts of the di- and mon-iodothyronines formed by decay However, 4 days after thyroxine biosynthesis, decay alone would result in the production of 12 0% each of the triiodothyronines, 1 0% each of 3,5-T$_2$ and 3′ 5′-T$_2$, 2 0% of 3,3′-T$_2$, and 0 45% each of 3-T$_1$ and 3′-T$_1$ Four days after a dose of 100 mC ^{131}I to a human subject or 100 µC to a rat, the two triiodothyronines, three diiodothyronines, and two monoiodothyronines should be detectable if formed by decay of thyroxine ^{131}I alone. In fact, most of these partially iodinated thyronines have not been detected in thyroid hydrolysates at any time interval after the administration of ^{131}I to man or

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1 Gross, J, Pitt-Rivers, R. *Lancet* 1951, i, 766
2 Gross, J, Pitt Rivers, R. *ibid* 1952, i, 439
3 Gross, J, Pitt Rivers, R. *Biochem J* 1953, 53, 645
4 Harington C. R., Pitt-Rivers, R., Querido, A., Roche, J, Taurog, A *Nature, Lond* 1957, 179, 218

experimental animals, although Roche et al.[5][6] have reported the presence of minute amounts of $3,3'5'\text{-T}_3$ and $3,3'\text{-T}_2$ in rat and pig thyroid hydrolysates. Whether all these iodinated thyronines are formed in the thyroid by decay or by some biochemical mechanism, and fail to be detected because of some rapid metabolic process still remains a possibility.

The work of Tata[7] on the effects of self and external radiations on ^{131}I synthetically labelled thyroid hormones provides some evidence that triiodothyronine is not formed from thyroxine in significant amounts by the decay mechanism proposed by Deutsch. Tata showed that the principal products formed from the labelled hormones during prolonged storage in solution were two unknown compounds, probably the lactic-acid analogues of the parent aminoacids, these in turn gave rise to no identifiable derivatives except iodide. Although radiation damage and decay would not result in the same breakdown products, one might nevertheless expect to detect some 3,5,3′-triiodothyronine if it had been formed.

For these reasons, it does not appear likely that ^{131}I-labelled thyroxine gives rise to significant amounts of ^{131}I-labelled triiodothyronine by decay of ^{131}I, whether the labelling is effected in vivo or in vitro.

National Institute for
Medical Research,
Mill Hill, N.W.7

R. C. HOLLOWAY
ROSALIND PITT-RIVERS

SHORTAGE OF DIETITIANS

SIR,—I was interested to read about the shortage of dietitians. On moving to Hertfordshire a few weeks ago I wrote to the divisional medical officer of health about possible employment as a dietitian. I did not even get a personal reply but was advised by the nursing officer to apply to the local hospital. They in their turn offered a nursing post. I am now working in a library.

J. BOLGER
Dietitian

TREATMENT OF URTICARIA

SIR,—Concerning last week's paper by Dr. Sidi and Dr. Reinberg, my own experience might be of value to others.

At Dr. Sidi's suggestion I undertook the course of treatment as described in his paper for chronic urticaria, and the results were entirely satisfactory and the condition disappeared, but at the end of the treatment I developed a very severe side-reaction to amodiaquine. This consisted of gastroenteritis followed by a severe attack of paroxysmal tachycardia necessitating a stay in hospital. All these symptoms fortunately disappeared but after three months the urticaria returned. As Dr. Sidi and his colleagues associated the therapeutic action in chronic urticaria with the antimalarial properties of the drug, I decided to try the effect of proguanil ('Paludrine'). In view of the extensive use of proguanil both during and after the war, and the almost complete lack of side-effects, I hoped that the drug would have the desired effect without any toxicity. I took 0.1 mg. twice a day for a week and the whole of my symptoms again disappeared and I stayed free of the condition for another three months. A slight return of symptoms occurred which were again dispersed by a similar course of proguanil.

I am of course well aware of the vagaries of this disease and also of the danger of drawing conclusions from one case.

Courtauld Institute of Biochemistry,
Middlesex Hospital Medical School,
London, W.1

E. C. DODDS

ACUTE HÆMATOGENOUS OSTEOMYELITIS

SIR,—I was very interested in the letter by Mr. Bremer and Dr. Neligan (Sept. 10) on the early and adequate exhibition of antibiotics in the treatment of acute hæmatogenous osteomyelitis. There can be no gainsaying that the administration of antibiotics in suitably large doses, within 48 hours of the onset of an attack of acute osteomyelitis, will, in the vast majority of cases, abort the attack, and render all operations unnecessary. Occasionally, however, an infection is so overwhelming that even very early treatment is of no avail—at least as far as the local progress of the disease is concerned. I had occasion to deal with such a patient three years ago in Canada.

A 14-year-old boy was seen by a pædiatrician because of severe pain in the right knee, with malaise and fever. These symptoms had developed very rapidly after a minor twisting injury to the knee, less than twelve hours earlier. The pædiatrician began treatment with penicillin, advising 250,000 units by intramuscular injection, four-hourly. A kaolin poultice was applied to the site of maximal tenderness in the upper third of the right tibia.

I was asked to see the child some six hours later, because pain and fever had increased, despite the local and general therapeutic measures. I found that he had a temperature of 102°F, and complained of severe boring pain in the upper right leg. Locally, there was some slight redness of the skin, very slight swelling, and exquisite tenderness. I advised that the dose of penicillin be doubled, and that local poulticing be continued.

Before the illness had lasted twenty-four hours, and despite the fairly large dose of penicillin, the child's temperature rose to 106.2°F, and he became wildly delirious at first, and later stuporose. A "lytic cocktail" of promethazine, chlorpromazine, and pethidine was given, and the child was cooled by exposure. Blood-culture showed *Staphylococcus aureus*, sensitive to penicillin, and indeed to the entire gamut of antibiotics.

Thirty hours after the onset of the illness, the child's temperature was 104.8°F, and there was much redness and swelling at the upper end of the right tibia. Pain was intense, and was scarcely relieved by the ingredients of the "cocktail", which had been continued. The decision to drill the tibia was made. At operation, no pus was found under the periosteum nor in the medullary cavity. *Staph. aureus* in pure culture was obtained from the medulla. The dose of penicillin was increased to 1 mega unit four-hourly. Chloramphenicol was now added to the assault, 3 g. intravenously in twenty-four hours. This regimen was maintained for ten days. During this time, the child ran an intermittent fever. There was insignificant drainage of pus from the tibial wound.

A further operation was therefore undertaken, and a segment of the subcutaneous aspect of the upper end of the tibia, measuring 3 in. by $^3/_4$ in., was removed. The wound was left open, and the limb encased in plaster of paris. *Staph. aureus* sensitive to penicillin was found in the medulla. There were no secondary contaminants. Chortetracycline was substituted for the other two antibiotics in a dose of 500 mg. four-hourly.

The story thereafter is one of subacute and chronic osteomyelitis, proceeding to massive sequestration of the tibial diaphysis, and involucrum formation. Eight months after the onset of the illness, I performed a diaphysectomy. Pockets of pus were found, containing *Staph. aureus*, still sensitive to penicillin. Fifteen months after the onset, the child was walking with the aid of a stick. The wound had healed, save for a small sinus track at the lower end.

It seems to me that the antibiotics saved this child's life, but they did not prevent the development of truly "surgical" osteomyelitis—possibly because the original septic thrombendarteritis was of such magnitude that no active antibiotic agent circulated near the organisms. At any rate, we did not upbraid ourselves at the time because

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5. Roche, J., Michel, R., Wolf, W., Nunez, J. *Biochim. biophys. acta*, 1956, 19, 308.
6. Roche, J., Michel, R., Nunez, J. *Bull. Soc. Chim. biol. Paris*, 1958, 40, 361.
7. Tata, J. R. *Clin. chim. acta*, 1959, 4, 427.

of inadequate treatment, nor do I do so now, looking back on the event I firmly believe that this case illustrates the contention that some infections are so overwhelming that even early adequate treatment will not preclude subsequent extensive surgery

Mayo Clinic,
Rochester, Minnesota
JOHN C CAMPBELL

WOLFENDEN AND BOXING

SIR,—Your leading article on the report of the Wolfenden committee on sport overlooks a point of medical concern—namely, that the committee apparently (p 3) regards boxing simply as one of a wide range of sports which are desirable and should be supported if necessary by public funds Would it not be more sensible to use public funds to enlighten the public about the dangers of boxing?

Department of Neuropathology,
Institute of Psychiatry,
Maudsley Hospital,
London, S E.5
F B BYROM
P M DANIEL

THROMBOTEST

SIR,—Mr Frohn and his colleagues (Sept 3) have prepared a thrombotest-like reagent, and conclude that such a reagent is inexpensive and not difficult to prepare It might follow from their work that the users of thrombotest should prepare their reagent themselves, and also that the commercial reagent is too expensive It is necessary to discuss this problem in some detail.

Anticoagulant therapy reduces mortality in coronary disease, rheumatic heart-disease, peripheral arterial disease, and in some forms of cerebral arterial disease Therefore, this therapy should be available to a large number of patients In most countries, however, only a fraction of such patients is now under permanent treatment

The main reason for this is probably the lack of a method specifically designed for the control of anticoagulant therapy Such a method must be theoretically sound, its results must be unequivocal and easily interpreted in terms of anticoagulant effect, it must be accurate, reproducible, and technically simple, and, finally, it must be generally available A coagulation laboratory may devise its own method and prepare its own reagents Experience has shown, however, that few laboratories are willing to accept this responsibility and labour Therefore, I devised the thrombotest method, and proposed that the reagent should be marketed to make it available to doctors who are prepared to undertake anticoagulant therapy

This reagent should obviously be inexpensive, otherwise it would not be generally available At present, the cost of the reagent is 9*d* for one test, or about 9*s* for one year's control (with one test every 4 weeks) This cannot be considered expensive

It is true that raw materials for the reagent are inexpensive and also that the production is fairly simple, if one does not insist upon absolute reliability (i e, complete absence of activation products), stability to storage, and uniformity between different lots Originally, we had to store the reagent deep frozen, since it was unstable on prolonged storage after lyophilisation This problem was finally solved in cooperation with the research laboratory of Nyegaard & Co A rigidly standardised production, however, and continuous control are necessary Each lot is stored for several months, and is released only when repeated tests have proved stability This makes the reagent more expensive, but I believe that these precautions are necessary for safe treatment It should also be pointed out that the actual expenses are often underestimated in a hospital laboratory which does not have to consider the cost of overheads, equipment, and labour

There are many analogies to this situation in the pharmaceutical industry For instance, we do not buy thyroid glands to prepare desiccated thyroid, or ox lungs to prepare heparin Nor do we make our own solutions for injection, and frequently we do not prepare our own sterile solution of glucose and saline The reason is that it is safer and more rational not to do it This, precisely, is the basis for the pharmaceutical industry

Nevertheless, I have asked the producer to reconsider the price At the present time, it is not possible to reduce it further If production can be further increased, however, it will be possible to reduce the price substantially

In reply to Colonel Groover (Sept 3), Dr Manchester's method [1] is essentially a prothrombin-time method in which equal parts of rabbit brain thromboplastin and capillary blood are mixed on a porcelain slide at room-temperature The normal value is 14–18 seconds It follows from my original paper [2] that this method is open to criticism both on theoretical and practical grounds, but I have no personal experience with his method

University Hospital, Oslo
P A OWREN

TRIAL OF A NON-SPECIFIC ANTI-CATARRH VACCINE

SIR,—I was interested in the conclusion reached by Dr Clark and Dr Grenville Mathers [3] that "trial of this non-specific anticatarrhal vaccine as a prophylactic against recurrent chest infection has shown it to be useless" My experience in a general pædiatric practice is contrary to this and more in keeping with that of Dr Compton (July 9), of the Wright-Fleming Institute, who states that "it is possible to control bronchitis prophylactically by repeated small doses of a vaccine, composed of respiratory bacteria"

We must distinguish between acute attacks of upper respiratory infection with pyrexia, conjunctivitis, bronchitis, and generalised muscular pain, and chronic or recurrent rhinitis and bronchitis without fever or malaise The former is likely to be, in at least 90% of cases, viral in origin,[4–6] while the latter, as Dr Compton states, is probably allergic and may be termed chronic or perennial allergic rhinitis and bronchitis It cannot therefore be expected that a bacterial vaccine, non-specific or autogenous, would be an effective prophylaxis against the virus infections The term "cold" leads to much confusion and should be avoided as it may indicate both viral and bacterial infections with catarrhal symptoms Parke Davis & Co, however, have recently produced a vaccine containing the adenovirus and polyvalent influenza virus ('Resprogen') designed to immunise against these infections

The administration of a bacterial vaccine composed of the common respiratory organisms is only one facet of the treatment in recurrent or chronic perennial allergic bronchitis and rhinitis My own approach, which is neither original nor unique and has proven very effective in my hands, is as follows

Congenital anomalies of the lungs and great vessels, agammaglobulinæmia, dysgammaglobulinæmia, and mucoviscidosis must be eliminated by appropriate investigation Unhealthy and infected tissue in the nasopharynx must be removed It would seem axiomatic that little improvement can be expected in this type of chronic respiratory illness in the presence of diseased tonsils and adenoids and infected sinuses It is difficult to comprehend the reluctance prevalent in some quarters in the removal of tonsils and adenoids in this malady We often hear from parents that whenever their child has a respiratory infection "it always goes to his chest or ears"

The allergic factor is of considerable importance and must be seriously considered Skin tests with the common allergens should be performed, and the majority of patients with chronic perennial bronchitis will show a positive reaction to many inhalants, especially house dust However, intradermal tests with extracts prepared from the common respiratory bacteria

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[1] Manchester, B *Ann interr Med* 1957, 47, 1202
[2] Owren P A *Lancet*, 1959, ii, 754
[3] *ibid* 1960 i 1416
[4] Dingle J H, et al *Amer J Hyg* 1953 58 16
[5] Evans A S *New Engl J Med* 1957 256 377
[6] Grieble, H G, et al *Amer J med Sci* 1958, 235, 215

(e g, *Neisseria catarrhalis, Streptococcus viridans, Klebsiella pneumoniæ*) may show a positive reaction only after 24–48 hours Examination of nasal mucus and sputum for cells and bacteria will reveal in allergic patients a predominance of eosinophils, and where infection is the major factor most cells will be neutrophils The administration of an anti-catarrh vaccine alone, therefore, to a patient who also is sensitive to other inhalants will not be very effective, while hyposensitisation with a combination of a respiratory vaccine and other allergenic extracts to which the patient has been found sensitive is usually successful If either of the extracts is to be used alone I suggest that the extract containing the common inhalants is the more important The bacterial respiratory vaccine I use is Sherman's no 39 containing 11 million organisms per ml consisting of

Klebsiella pneumoniæ (Friedländer bacillus)	100 million
Hemophilus influenzæ (influenza bacillus)	200 million
Diplococcus pneumoniæ (pneumococcus)	100 million
Streptococcus (viridans, hæmolytic, and non-hæmolytic)	100 million
N catarrhalis (Misc catarrhalis)	200 million
Staph aureus	200 million
Staph albus	200 million

commencing with 0 05 ml subcutaneously, increasing to 0 5–1 ml depending on age, given at weekly intervals

Thus, the removal of infected tissue in the nasopharynx, the performance of skin tests, and hyposensitisation with a bacterial respiratory vaccine and an extract of other appropriate allergens, will improve the majority of patients with chronic and recurrent allergic bronchitis and lessen the need for the " cough bottle "

Scarborough,
Ontario

NATHAN SHER

SPONTANEOUS FRACTURE OF THE FIBULA

SIR,—A woman of 68, a retired " companion ", was out walking one evening last December when she felt a sudden pain above her right external malleolus

She had not kicked, twisted, or otherwise harmed her leg, and, thinking it was a progression of the osteoarthritis she had had in both knees for 15 years, she continued walking That night the ankle was swollen but not bruised, and the pain was unrelieved Rest eased the pain, but it was aggravated by walking For 2 months she managed to continue her normal life, but finally she came to hospital

On admission, under the care of Mr D Lang Stevenson, pain was still present She had varicose veins in both legs, having had a long saphenous strip on the left in 1949 A small tender lump was palpable 2½ in above her right external malleolus There was no œdema A thrombosed vein was diagnosed tentatively, and an X-ray was taken This showed a recent transverse fracture, with normal callus, 2½ in from the tip of the external malleolus (see figure)

The interest of this case lies in the fact that a non-weight-bearing bone fractured spontaneously without trauma The patient had no general decalcification, as shown by comparison of her hand X-ray with that of a 66-year-old control, and there were no signs of metastatic deposits or myelomatosis

Jackson Burrows,[1] in a review of the published reports on this subject, found 20 cases which could be divided into two main groups (1) Young men undergoing unaccustomed exercise, such as infantry training, road-running, or ice-skating, and (2) Middle-aged women taking a fair amount of exercise, but usually without any great increase in exercise at the time of fracture (5 cases) The young men had fractures more than 2 in above the tip of the external malleolus, while the women's fractures were all 1½ in above No reason for the difference was put forward My patient's fracture, unlike those in Jackson Burrows' second group, was more than 2 in above the tip of the external malleolus

No adequate explanation of these " fatigue " fractures has been put forward The bowing and springing of the fibula, demonstrated by Devas and Sweetnam,[2] when weight is put on the leg and then released, shows the forces acting on the bone But this does not explain why one bone breaks and another does not Could it be that, during fatigue, muscle coordination is diminished and the bone suffers abnormal and contrary stresses, and so breaks ? This would tie up with the fractures from abnormal exercise in young men

Whipps Cross Hospital,
Leytonstone, London, E 11

G A HOBBS

THE SERIOUSLY ILL PATIENT AND THE HELICOPTER

SIR,—Dr Skone and Dr Mills, in their interesting paper of Aug 13, briefly review the occasions on which helicopters have been used for air-rescue May I remind them of another remarkable operation—the combined action against Port Said in 1956 On this occasion more than 70 casualties were evacuated to aircraft carriers in a single day It was possible for a combatant to be transported to the front line, suffer a wound, and return to " base " all in the space of half an hour The medical aspects of this extraordinary affair were discussed by Gosling et al [3] and by myself [4]

London, W 1

R I BODMAN

DEATH AFTER OVERDOSE OF IMIPRAMINE

SIR,—I wish to record a case of suicide by overdose of imipramine (' Tofranil ') and to publicise the possibility of a fatal outcome

A woman of 29 was under treatment for depression and was being given 6 tablets (25 mg each) of imipramine daily On Aug 8, 1960, at 8 A M when her husband awoke she told him she had taken all her tablets (estimated by the husband, who normally kept them, at between 60 and 80 tablets) The husband immediately rang for the ambulance and the police She, meanwhile, became incoherent and restless and was then removed to the local hospital

Here Dr R M Turner described her as stuporose and unable to answer questions She was cyanosed and her blood-pressure was 100/60 mm Hg, which was known to be lower than her normal blood-pressure The stomach was washed out apparently successfully but the washings were not available for subsequent analysis

At 10 A M she had a typical grand-mal convulsion, and after a short pause convulsions resumed and continued until her death at 10 30 A M Post mortem no significant anatomical changes were noted

Chemical analysis was performed by the Home Office Laboratory at Gosforth, Northumberland, under Dr H J Walls The stomach contents produced only 19 mg of imipramine, the blood only traces, and the urine none. The liver contained only 1 25 mg per 100 g The recovery of the

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1 Burrows, H J *Bone Jt Surg* 1948, 30B, 266
2 Devas, M B, Sweetnam D R *Practitioner*, 1958, 180, 340
3 Gosling, R. E G, Main, P T, Paros, N L *ibid* 1957, 179, 191
4 Bodman, R I *J R Army med Cps*, 1958, 104, 179

drug is poor, but this is partly due to the loss of the stomach washings In part it is also due to the labile nature of the drug Dr Walls has found similar low recovery-rates in previous cases

Hypotension due to imipramine is widely recognised, and epileptiform convulsions have been described in 2 patients who had taken a large overdose[1 2] Levene and Lascelles[2] controlled the fits by paraldehyde, and the patient recovered The cyanosis noted by Dr Turner does not seem to have been emphasised by previous authors

Ashington Hospital,
Northumberland

T MANNERS

MIDDLE MENINGEAL HÆMORRHAGE, THE GENERAL SURGEON, AND THE NEUROSURGEON

SIR,—May I correct some of the misconceptions in your annotation of Oct 1? With regard to the part played by the general surgeon, it is certainly not intended that carotid angiography should be done in a general hospital, and I have indicated that cases of extradural hæmorrhage may be so urgent that time should not be wasted on even a plain X-ray of the skull

Your statement that " not all critically ill patients will withstand the operating-time and blood-loss involved " in a craniotomy can be answered simply, the turning of an osteoplastic flap when the dura mater is already stripped by hæmorrhage takes about ten minutes (I have done it in seven), and the blood-loss amounts to perhaps one ounce with a practised assistant, double that amount with an inexperienced one

Brook General Hospital,
Woolwich, London, S.E 18

J R GIBBS

ESSENTIAL HYPERTENSION

SIR,—Dr Morrison and Professor Morris raise several questions that need answering at leisure with my colleagues Meanwhile may I ask

(1) Are the legends of figs 2 and 3 correct?

(2) Would they kindly provide evidence for their important statement " Moreover the cases of essential hypertension behave so homogeneously that it is reasonable to postulate they consist predominantly of a specific disease entity " This evidence has hitherto been concealed from me

Oxford.

GEORGE PICKERING

*** We are sorry to say that the answer to Sir George's first question is " No," and we apologise to Dr Morrison and Professor Morris and to all those who were perplexed by the mistakes explained in the corrigendum on p 938 —ED L

SIR,—Dr Morrison and Professor Morris, discussing the resemblance of blood-pressure between relatives (Oct. 15), stated that " at high levels of blood-pressure there is little if any graded relationship between the height of the pressure in individuals and their first-degree relatives "

In a paper a year ago,[3] I studied this problem According to the equation $y=a+bx$, I found a regression coefficient b of 0 277, when I plotted the diastolic blood-pressure of 14 " essential hypertensive " patients (mean age-adjusted score, +39 0±7 18) against the diastolic pressures of 39 of their first-degree relatives (mean age-adjusted score, +10 0±1 81) Furthermore, the correlation coefficient r of Pearson I found to be 0 512

Because these two coefficients were significant I concluded that there exists at high levels of blood-pressure a graded relationship between the height of the pressure in individuals and their first-degree relatives

Hospital Aguirre,
University of Chile School
of Medicine, Santiago

R CRUZ-COKE

THE VERY DEAF CHILD

SIR,—Please allow me to assure Miss Whetnall (Oct 15) that as a member who helped to formulate the resolution of the Association of Non-Maintained Schools for the Deaf, deploring the placing of profoundly deaf (grade III) children in units for partially hearing children, I was familiar with both its content and the factual evidence presented at the meeting when the resolution was unanimously approved

It is true that I made no reference to partially hearing units in my letter of Oct 8 because, as Miss Whetnall says, a full discussion in *The Lancet* would be out of place and certainly irrelevant to my criticism of your annotation of Sept 17 I would, however, affirm that both the Ministry of Education and my college have frequently stated that whenever possible partially hearing and profoundly deaf children who fall into the grade-IIB and grade-III categories should be educated separately

Miss Whetnall's assertion that my letter shows a lamentable ignorance of the so-called " auditory method " as illustrated by the work of Wedenberg cannot go unchallenged Perhaps she will present " chapter and verse " for this statement As a former Medical Research Council psychologist, in my studies of the mental abilities and educational achievement of deaf children, I made a detailed study of the Erik Wedenberg method[1 2] Even Wedenberg, unlike Miss Whetnall, admits that there are " auditory " failures, especially in the case of children with an excessive flat hearing loss or those without any auditory feedback whatsoever These children were transferred to schools for the deaf following the experiment

I find it most difficult to reconcile Miss Whetnall's apparent advocacy of Wedenberg principles—i e, his method of merely speaking close to the child's ear—with her own publicly reported recommendation that deaf babies in cots should be provided with hearing-aids, thereby avoiding the possibility of them being sent to special schools, where their residual hearing would not be stimulated

It is my firm belief that any expert in our field, either in clinics, schools, or other establishments, should be most careful not to overstate the effectiveness of Miss Whetnall's so-called " auditory " method with profoundly deaf children, even on the basis of a few successful cases, translated into universal types Some day enlightened medical, educational, and parental bodies will catch up with exaggerated claims, but only unfortunately after the tragic disillusionment of many parents of deaf children for whom the great " auditory experiment without lip-reading " did not work out so well

Miss Whetnall's classification of deaf children is less acceptable than the Board of Education's 1938 recommendations because it pays no attention to onset of deafness, which can occur at any age, and the many other important factors, so admirably stated in Mr Shorrock's letter of Oct 15 In concentrating upon the medical aspects of hearing loss, there is also a distinct danger of minimising the importance of acquiring those specific skills teachers need to acquire to train severely deaf children most effectively The educational and social

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[1] Brooke, G , Weatherly, J R C *Lancet*, 1959, ii, 568
[2] Levene, L. J , Lascelles, C F *ibid* p 675
[3] Cruz Coke, R *Rev med Chile*, 1959, 87, 699

[1] Wedenberg, E *Acta otolaryng , Stockh* 1951, suppl 94
[2] Wedenberg, E. *ibid* 1954, suppl 110

needs of deaf children cannot be met by the simple process of talking into a baby's ear or the provision of a transistor hearing-aid

Royal Cross School,
Preston

Peter Gaskill
Press Relations Officer,
National College of Teachers of the Deaf

MORE CHROMOSOME ANOMALIES

Sir,—In a leading article of July 23 you state, referring to our work [1] on the single-X nature of the sex chromatin, " that in the female rat only one chromosome (as seen in prophase) is heterochromatic " This is a misstatement of our discussion Both X chromosomes in the female rat and the X and the Y in the male are heterochromatic The heterochromatic nature never varies What does vary is the behaviour of these chromosomes in relation to the autosomes during various stages in the life-cycle of individual cells In somatic cells of the female, during interphase and prophase one of the two X chromosomes is positively heteropyknotic—more condensed and deeply staining—than the other X chromosome and the autosomes Heteropyknosis is not a constant property of heterochromatin but seems to depend upon the characteristics of the individual cell More recent work has shown that in the prophase of rat oocytes the two X chromosomes are isopyknotic to the autosomes In males the situation is reversed Somatic cells are chromatin-negative, but the sex pair in the prophase of first meiosis is heteropyknotic

Department of Genetics,
City of Hope Medical Center,
Duarte, California

William D Kaplan

TOBACCO MOSAIC VIRUS AND LUNG CANCER

Sir,—I followed with great interest the discussion in your columns about a possible connection between lung cancer and tobacco mosaic virus (T M V) Since 1956 I have conducted a series of skin tests with T M V on men and animals

(1) With T M V I studied skin reactions at high dilutions of 1/7 × 1 5 × 100 * intracutaneously in 72 subjects (smokers and non-smokers) The results were completely unexpected In 23 confirmed regular smokers no local reaction was observed in the arm injected In 49 non-smokers an intense local reaction appeared with a peculiar " neuralgia " extending to the axilla Intense positive skin reactions to T M V were also observed in patients with virus infections, especially parotitis

(2) Distinct precipitation in smokers and indistinct changes in non-smokers were observed in serum tests with smokers' and non-smokers' sera diluted 1/20, 1/10, 2/10, with diluted virus in distilled water 1/7 × 1 5 × 100—that is, with 1 µg of virus

Abundant precipitation was observed with sera of patients with acute rheumatism, and precipitation was also observed in virus infections, again particularly in parotitis The precipitation in acute rheumatism and parotitis was so distinct that I proposed it as a diagnostic test in these diseases

(3) In lung cancer both skin reactions and the precipitation were intensively positive

I vaccinated tobacco leaves with cancerous matter taken by paracentesis from the lungs Tobacco mosaic disease developed in 3 out of 4 cases In spite of precautions I might have infected the leaves myself, since I am a smoker, and the virus might also have got into the patients' respiratory tracts The mosaic virus may enter the lungs not during the burning of the tobacco but in small unburned pieces of tobacco during violent inhalations, in saliva, or during sleep

The virus was provided for me by Mr B Kassamis, assistant to Sir William Ogg at Rothamsted Experimental Station

Infectious Diseases Hospital,
Athens

Lambros Katsilambros

Obituary

JOHN MARTIN MUNRO KERR

M D , LL D Glasg , F R F P S , F R C O G

Few men have seen so much change in their lifetime as Munro Kerr, and even fewer have themselves done so much to bring about that change By his teaching in the regius chair of midwifery at Glasgow University and by his textbooks, which were read all over the world, he did much to raise the standards of obstetric practice and to make childbirth safer for mother and baby

He was born in 1868, the son of a Glasgow shipowner, and he was educated at Glasgow Academy and Glasgow University Soon after qualifying in 1890 he decided to specialise in obstetrics and gynæcology, and he spent several years in postgraduate study at the Rotunda Hospital in Dublin and in Jena and Berlin In 1894 he became assistant to the regius professor of midwifery at Glasgow He was appointed visiting surgeon to the Royal Maternity Hospital in 1900 and gynæcological surgeon to the Western Infirmary in 1907 He became professor of midwifery and gynæcology at the Anderson Medical College in 1910, and the following year he became the first occupant of the Muirhead chair of obstetrics and gynæcology

Annan

He succeeded to the regius chair in 1927 On his retirement from the teaching staff in 1934 after forty years' service, the university conferred on him the honorary degree of LL D He was one of the founders of the college of his specialty and was its first vice-president In 1948 when the college was granted a royal charter the honorary fellowship was conferred on him In his own city he served as president of the Royal Faculty of Physicians and Surgeons from 1933 to 1936 In 1950 he was the first Blair-Bell medallist

His first outstanding book *Operative Midwifery* (later known as *Operative Obstetrics* and now in its 6th edition under the editorship of Prof Chassar Moir) first appeared in 1908, and for this classical work his own university awarded him the degree of M D with high commendation The *Combined Textbook of Obstetrics and Gynæcology* (1923), for which he was largely responsible, was a new departure which did much to wed obstetrics to gynæcology In 1933 he was awarded the Katherine Bishop Harman prize for his monograph on *Maternal Mortality and Morbidity*

Soon after he retired he settled in Canterbury, and during the late war he turned again to medical work and acted as medical superintendent to the Kent and Canterbury Hospital Even after he finally gave up practice he continued to contribute to medical journals In his later years he missed his visits to London libraries, but he was never idle, and he wrote reminiscences and historical sketches Only four years ago he travelled overnight to Glasgow to give the first William Hunter memorial lecture at the Royal Faculty of Physicians and Surgeons, and a friend who visited him on his 90th birthday found that the " old sparkle, charm, and elegance were still there, and at the end of two hours we were talking furiously and many of his questions had to remain unanswered " He died on Oct 2 within a few weeks of his 92nd birthday

D B , who was his first registrar, writes

" Like his great friend, Sir Robert Muir, Munro Kerr was well endowed with that essential quality of a leader, the ability to attract and inspire the young. He trusted his juniors and gave them responsibility, and in consequence they worked hard and were extremely loyal. He was interested in their routine work and in their researches, gave them introductions to his many colleagues at home and abroad, and was a wonderful host. He was even prepared to give useful hints on such personal matters as the proper choice of a wife. Good looks, elegance, charm, vivacity, and freedom from affectation were allied to mastery of his professional and administrative duties. Our affection for him was not diminished by his occasional outspokenness and impulsiveness. A junior who let him down was told so in no uncertain terms. He was prepared to fight for what he thought right, and sometimes made an enemy unnecessarily when a little guile might have achieved as good or better results. But his department remains in my memory as a friendly, cheerful, and stimulating place.

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[1] Ohno, S , Kaplan, W D , Kinosita, R *Exp Cell Res* 1959, 18, 415

* 1 5 ml of T.M V sample (1/7 virus in 1 ml) diluted 100 times

"His patients loved him no less than his staff. Whether in his hospital or his private practice, all were treated with equal courtesy and consideration. He would address the toughest inhabitant of Glasgow's slums as if she were a duchess. It was most amusing, before his ward round in 'Rottenrow', to watch the patients making active sartorial preparations.

"M. K. was a great personality. The Glasgow tram has always been an interesting place but never more so than when Munro Kerr rode on it along Parliamentary Road to the Royal Infirmary, dressed in a cutaway morning coat, light waistcoat, cravat, long overcoat with black astrakhan collar, spats, and bowler hat, and, to complete the picture, a monocle. As he measured about 6 ft. 1 in. it can be imagined how he stood out amongst the stunted people who thronged the streets in that neighbourhood. Now they are being replaced by a more healthy generation, and as their numbers dwindle, so the art and science of obstetric surgery are giving place to those of obstetric medicine. Many of the emergencies which Munro Kerr wrote about so well and so vividly are fading into history, but he was admirably equipped to deal with the urgent problems of his day and, in addition to being a great obstetrician, was a great man. The inspiration he gave will remain with all who knew him."

Turning from professional attributes and distinctions, R. A. L. asks what was the manner of the man?

"Debonair, blessed with great personality and charm, a sense of humour, a good clubman, and socially in his element when among his friends—these traits distinguished him as a great gentleman. We well remember the official and social duties he so ably performed at the Rotunda Congress. There he was at his best—friendly to all, forever charming and accessible to those from overseas who knew him by repute but who had never met him in person."

J. C. M., who heard in Trinidad of the death of his "friend and mentor", writes:

"At the end of the century Glasgow was an industrial city notorious for the prevalence of malnutrition and of rachitic deformities. The suffering of women in childbirth would, to our younger generation of obstetricians, seem unbelievable. Craniotomy was an almost daily necessity, rupture of the uterus and extensive sloughing of the vagina were commonplace, and even if such horrors were avoided, many a woman was ruined in health for the remainder of her life. It was against this background that Munro Kerr saw some of the first cæsarean operations performed in this country. They made a deep impression on his young mind, and henceforth much of his energy was directed to improving the safety of the operation. The result was the lower-segment approach with the transverse uterine incision, and in this innovation he was undoubtedly a pioneer.

"In the early 'twenties only a few of the younger surgeons in Glasgow and Edinburgh were hesitatingly employing the operation, by the 'thirties it had gained ground but was still largely ignored by obstetricians in the south, yet today it is universally acclaimed, and is almost always the method of choice. This complete change was made clear in 1949 at the first post-war obstetrical congress. Speaker after speaker had shown the increased safety of cæsarean section, but none had clearly stated why. Then Munro Kerr, recognised among the audience, was quite unexpectedly called on to address the assembly. As the tall, lean, figure, immaculately dressed, advanced to the platform, necks were craned, for many present did not realise that this well-known name was still borne by a living man. No address could have been shorter or more dramatic. Referring to the previous speakers and the lower-segment operation, he threw up his arms and in a loud voice exclaimed 'Hallelujah! The battle's o'er, the victory's won!'

"Despite dramatic moments such as this, he was not a fluent speaker, but he was more gifted and skilled than any man I have known in the art of writing with absolute clarity, and in a manner that would interest—even enthrall—the reader. The success of *Operative Obstetrics* was due not only to the soundness of its teaching, but also to his delightfully intimate and conversational style. He told me that in the first place he dictated each chapter while striding to and fro in his room, and if later he painstakingly perfected the text, he never interfered with its apparent spontaneity.

"Charm of manner was coupled with a firmness, but honesty of purpose. 'All compromise is immoral', he would say, yet no one was more ready to listen to reasoned argument. These qualities, together with his kindly interest in the welfare of others, and especially of his junior colleagues, will ever be my abiding memory of this great man who, more than any other of his generation, shaped British obstetrics."

Professor Munro Kerr married in 1899 a daughter of August Johanson, of Gothenburg. She died in 1957, and they leave a son and three daughters.

Appointments

BIRNSTINGL, M. A., M.S. Lond., F.R.C.S.: part-time consultant in general surgery, St. Bartholomew's Hospital, London.

LAUCKNER, J. R., M.B. Edin., M.R.C.P., F.R.F.P.S.: deputy physician-superintendent (S.H.M.O.), Holywood Hall Hospital, Wolsingham, Bishop Auckland.

NAPIER, ISABELLA R., M.B. Edin., M.R.C.O.G., D.P.H.: assistant M.O., Ealing and Acton.

Liverpool Regional Hospital Board

EDWARDS, D. N., M.B. Lond., D.M.R.T.: assistant radiotherapist, regional radiotherapy service.

FORSHAW, J. W. B., M.D. Cantab., M.R.C.P.: consultant physician and deputy medical superintendent, Sefton General Hospital.

FRASER, K. M., M.B. Lpool, D.C.H., D.P.M.: consultant in child psychiatry, Alder Hey Children's Hospital.

HOPKINS, C. A., M.B. Lpool, M.R.C.P.: consultant chest physician and deputy physician-superintendent, Aintree Hospital.

HUGHES, H. J., M.B. Wales, D.M.R.T.: assistant radiotherapist, regional radiotherapy service.

ROBERTS, J. R., M.D. Lpool, M.R.C.P.: part-time consultant pædiatrician in neurology, Alder Hey Children's Hospital.

Manchester Regional Hospital Board

BROWN, J. M., M.B. Lpool, D.M.R.D., F.F.R.: consultant radiologist, Preston and Chorley group of hospitals.

CARSTAIRS, L. W., M.D. Durh., M.R.C.P.: consultant chest physician, Burnley and district group of hospitals.

DAVIES, V. J. E., B.M. Oxon: assistant pathologist, Oldham and district group of hospitals.

DOYLE, LESLIE, M.B. Dubl., M.R.C.P.I., D.C.H.: consultant chest physician, South Manchester group of hospitals.

ELLIDGE, G. H., M.B. Lpool, M.R.C.O.G.: consultant obstetrician and gynæcologist, Bury and Rossendale group of hospitals.

LOUGHNANE, THOMAS, M.B. Dubl., D.P.H., D.P.M.: assistant psychiatrist, Whittingham Hospital, near Preston.

LYALL, THOMAS, M.D. Aberd.: consultant venereologist, Stockport and Buxton, Macclesfield and district, South Cheshire and Salford groups of hospitals.

SIMS, A. J., M.B. Lond., F.F.A. R.C.S., D.A.: consultant anæsthetist, Bury and Rossendale group of hospitals.

WILSON, E. H., M.D. Lpool: consultant geriatrician, Lancaster and Kendal and Lancaster Moor groups of hospitals.

Colonial Appointments

BATHFIELD, C. A., M.B.E., G.M., F.R.C.S.E.: medical superintendent, health department, Mauritius.

CAMPBELL, N. G. D., M.B.E., M.B. Cantab.: senior M.O., Sierra Leone.

CONWAY, G. F., M.B. Polish Sch. of Med., Edin.: M.O., Kenya.

EDGDELL, H. C., M.B. Leeds: M.O., Uganda.

JONES, T. R., M.B. Lond., D.P.H., T.D.D.: tuberculosis officer (M.O.), British Guiana.

KACHAN, P. R., L.R.C.P.I.: M.O., British Guiana.

LOWRY, D. M. O., M.R.C.S., D.P.H., D.I.H.: D.D.H.S., Bermuda.

MOORE, A. R., L.R.C.P.I., D.T.M. & H.: pathologist, Tanganyika.

NELSON, G. S., M.D. St. And., D.T.M. & H.: specialist (senior parasitologist), Kenya.

RENEAU, J. A., M.D. Guatemala, M.P.H. Puerto Rico: M.O.H., British Honduras.

WHITTAKER, L. R., M.R.C.S., D.C.H., D.M.R.D.: specialist (radiologist), Kenya.

Notes and News

A GUIDE TO BRITISH HOSPITALS

As anxieties mount concerning shortage of junior hospital staff, many hospitals are looking with new eyes on such things as married quarters, organised postgraduate training, and residents' food and hours of work From the young doctor's point of view what has long been needed is a guide to National Health Service hospitals to supplement the information in the *Medical Directory*, and this the British Medical Association has now admirably provided by means of a fairly comprehensive but inexpensive *Hospital Gazetteer*[1] This very useful book should be at the right hand of anyone seeking a junior appointment in a hospital unknown to him

After recording the bed numbers and describing the special departments, the gazetteer gives the postgraduate diplomas for which the hospital is recognised and the total staff complement, senior registrars down There follows a rather uncertain account of rotas, locums, and off-duty, and the type of accommodation available Finally there is a synopsis of the amenities —parking, television, games, library, and so on

Though most of the factual returns from hospitals have been adequate and agreed by both the junior staff and the hospital authority, the completeness of the record varies much, and occasionally its accuracy may be questioned Bitter laughs may be raised by the statement that the staff of such-and-such a hospital is " normally full strength ", but a few returns do admit that this happy state is unusual The omission of all psychiatric hospitals, sanatoria, and some cottage hospitals is the largest deficiency, which later editions may be able to make good As an addition to the useful details of postgraduate diplomas at the end of the book, the Ministry circular (H M 58/18) on standards of accommodation might also have been reproduced And the matter of junior representation on medical staff committees could have been raised It might ultimately be possible to give an idea of the *quality* of training, experience, and accommodation A 5-star system would be hard to devise, but some rating scale, perhaps on several parameters, should not be impossible

Apart from its informative value for junior staff, the gazetteer is very welcome as a guide to hospital administrative practice, and as an incentive to slow committees to improve their terms and conditions Teaching hospitals often say " no official off-duty ", and non-teaching ones " 1/2 day p/w, 1 w/e in 3 " Is this adequate?

CONCLUSIONS ON TUBERCULOSIS

A SEMINAR held some months ago in Sydney at the School of Public Health and Tropical Medicine under the auspices of the World Health Organisation was attended by representatives of 26 South-East Asian and Western Pacific countries as well as Australia and New Zealand Below we summarise some of the conclusions drafted after animated discussion

Two-drug therapy is best for the treatment of the active case and should be continued for at least twelve months When this is not possible, attempts should be made to give three months' two-drug therapy followed by isoniazid alone for nine to twelve months Though two-drug therapy is preferable, the use of isoniazid alone is acceptable where insistence on the use of a companion drug would greatly limit the scope of a domiciliary programme As no definite advantage of three-drug therapy has yet been demonstrated in man or laboratory animals, and the holding of P A S (*p*-aminosalicylic acid) or streptomycin in reserve has certain advantages, the practice of three-drug therapy is not to be encouraged except in fulminating tuberculous disease

The recommended daily dose for an average man is isoniazid, 300 mg , streptomycin, 1 g , P A S , 10 g

There is a trend towards giving isoniazid alone for the treatment of potentially active cases, cases with slight lesions, and those with moderately advanced lesions without cavity or with cavities less than 3 cm in diameter It may also be used for follow-up therapy in patients who have responded favourably to two-drug therapy In whatever way isoniazid is given, some isoniazid-resistant bacilli may eventually appear, but possibly because some are different from normal bacilli, this has so far not proved to be an epidemiological problem

A failure-rate of 10–15% may be expected with chemotherapy alone Some of the failures may be suitable for surgery, while others may respond to the " secondary " drugs, but a hard core of positive patients will remain

If beds are available, a preliminary period in hospital in valuable for assessment, intensive combined therapy, and education, but in most instances properly supervised domiciliary care has been satisfactory Surgery, while playing an important part in the treatment of the selected patient, is of minor importance from the public-health point of view Steroid therapy has limited application in the treatment of tuberculosis

Laboratory tests on drug resistance are of great value in assessing the epidemiological situation in a community But in the treatment of an individual patient they are a refinement which, while sometimes helpful, is not essential in the management of chemotherapy programmes

The prophylactic use of isoniazid in tuberculin reactors without obvious disease is recommended as follows (1) in all infants and preschool children who are " natural " reactors to tuberculin, (2) in all children who are reactors at school entrance and who have not received B C G since shortly after birth, (3) in schoolchildren and adolescents (a) where surveys show a relatively high prevalence of tuberculosis in those aged 6–12 or 12–20 years, (b) in those whose tuberculin reaction to a standardised dose of tuberculin is large, and (c) in household associates of patients treated at home, and (4) in tuberculin reactors at any age who presumably represent " poor hosts ", such as diabetics, silicotics, and persons receiving steroid therapy for non-tuberculous disease

The observation that the resistance of laboratory animals to a challenge infection can be greatly influenced by varying the ratio of aminoacids in the dietary protein may prove a most valuable clue

Contacts must always be followed up by the usual methods, and negative tuberculin reactors given B C G Chemoprophylaxis should be given to positive reactors under the age of 6 and to all patients with a florid reaction

THE DEVELOPMENT GROUP

THE Ministry of Health Development Group is losing three of its architectural staff to university and regional hospital board appointments

Mr P D Cowan is to carry out research into the " balanced hospital community " at University College, London, under the direction of Professor Llewelyn Davies, Mr R O Moss has gone to the South East Metropolitan Regional Hospital Board as a principal assistant, and Mr V H Lee joins the North West Metropolitan Board shortly as deputy regional architect

The Ministry rightly says that this movement of staff between itself and university and board posts is healthy, but it will necessarily slow down the work of the development group The Ministry is now advertising for additional staff

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University of London

At recent examinations for the D P H the *following* were successful

Umberto Broccolo Tommasi, W J E Darling, E D *O Okeke*, Diljit Gur Bachan Singh, Nadir Tekirli, Joyce D Waye, Jean B Wickings

University of Aberdeen

Dr J A Shanks has been appointed to a terminable lectureship in patholgy and Dr G A German to a *research* fellowship in physiology

Association of Clinical Biochemists

The following officers have been elected

President, Dr C P Stewart, chairman, Dr A L Latner, hon treasurer, Dr R Gaddie, hon editor, Mr H Varley, hon secretary, Dr J H Wilkinson (Westminster Medical School, Horseferry Road, London, S W 1)

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[1] The Hospital Gazetteer London British Medical Association 1960 Pp 163 5*s* (by post 6*s*)

Royal College of Surgeons of England

At a meeting of the council on Oct 13 with Sir Arthur Porritt, the president, in the chair, Prof Erling Dahl-Iversen (Copenhagen) and Prof Jan F Nuboer (Utrecht) were elected to the honorary fellowship Prof L N Pyrah was admitted to the council and Mr Charles Keogh to the court of examiners

Dr C Jackson Rees and Dr A I Parry Brown were admitted to the board of examiners for the fellowship in the Faculty of Anæsthetists

A diploma of fellowship was granted to S M. Cameron and Prakash Narain Tandon, and diplomas of membership to P B Evans, M T Jones, and K Kyei-Mensah

Diplomas of fellowship in the Faculty of Anæsthetists were granted to the following

Denis Wakely, B R Whittard, D S Hutton, Cecil Bishop, D C Jackson, J E S Relton, D W Atherley, G J Taylor B R P Murray, J E Utting, Zbigniewa A. Jordan-Sikorska, Andrzej Maciejewski, L J F X Dunkin, A S McC Lamont, James Cox, P B D Souza, Maureen E Hardeman, K G Smith, Raghubar Prasad Badola, M E H Barrow, T H Howells, S W McGowan, Cyril Ward, S J S Webb, Ming-Hon Yeung, Joseph Baldasera, F E Bennetts, R A Browne, G H Bush, E R J Emery, Ruth Hutchinson, T N Munro, I S Paterson, H G Pledger, J W Sandison, J P Alexander, Noormohmed Haji Ahmed Doctor, Sylvia Lock Seung Hui, J D Kinnell, R. N Lewis, W T McNeil, D S Robbie, G T Spencer, J G Whitwam, A D Crew, D G Larard, Audrey M Peeling

The following diplomas were granted jointly with the Royal College of Physicians

D L O—G Chattopadhyay
D I H—A K Sen Than Myint
D M.R.D—G I Verney
D.P.M—G F Burke, A McQuaid
D.A—C K Davies
D.Phys.Med—G M Cochrane, Joan M Evans, Shona Hodgson, E. A Kauffmann, D R D B Kulatunga, D Y Mackenzie, D A H Yates

D T.M & H—Debabrata Bagchi, J S Bailey, Hikmat Baquir, J D Barrett P A Baumann K A Beahan, F E P Bernard, E G A Bernez, J H Bradshaw-Smith, K R Dalley, M H Davies, F L Dunn, W R O Eggington, W O C FitzPatrick, Mohamed Abdul Gaffar, F C Grant, John Grant, Md Nasirul Haque, A J M Hargreaves, Javid Azim Hashmi, Heini Marikka Hintsanen, Martin Houmoller-Jorgensen, R A Iles, Fazaluddin Jatoi, Ursula Jehles, Haq Nawaz Khan Ahmed Amin Ahmed Khallaf, Sukumar Chandra Kundu, J W G McDougall, W P Maclay, Vibhakar Moreshwar Joglekar, Norman MacLean David McSwiggan, Narges Mahaluxmivala, Mashkoor Ahmed Marghoob, W C Moffat, J G Moran Sanat Kumar Mukherjee, Lewis Mullins Amarut Na Songkhla, Yash Prakash Narula, N W Nicholson, Hamid Noorparvar, J W Norris, P L. Pearson, Nomal Chandra Pegu, Mohammad Habibur Rahman, R. J Read, M. A Rozalla, Saif-Ul-Haque, A J Salter R R Schenck, Md Maswood Alam Shams, Shambh Sharan, Gur Gyan Singh, Binod Behari Sinha, G L Smith, P J Stevens, Antoni Wladyslaw Swiecicki, Iraj Tabibzadeh, S B Telford, William Wagstaff, J G Winwick

D O—Ghulam Naseeruddin Ahmed, Selig Percy Amoils, J D C Anderson, Jitendra Lall Banik, J H Cameron, J S Cant, A J Chadwick, Deoram Khandoo Chaudhari, Vyankatesh Mahadeo Deval, W N Dugmore, F X Fernandez, D P Gale W G Gaston Norman Gibbons Florence C Gordon, Melody J Grice, R M Halley, R H S Hellein, Thevakadadchavathy Hoole, Yousuf Husain, Behman Hormasji Irani, Samindra Nath Kalita, J H Kelsey, Jayant Balkrishna Kelshiker, B R Kesby, Tej Kohli, P J Kriel Raymond Levy, W C Logan, J D C Macdiarmid, M B R Mathalone, Mohomed Bashiruddin Mehkri, J H Rickeard, I R Robertson, Beohar Ramsujan Sinha, E J Sinton, Asghar Ali Syed T A J Thorp, Luke Shu-Ling Tsai, Sinnappoo Velauthan, Rene Wiss, Mohammad Yaqin

D C H—J E J Aiyathurai, W W Akroyd, Shadida I Ali, Ishaya Sha Aibu Audu, S J Azzopardi, Biplab Kumar Basu George Beaumont, Felicity M Bedford, Kulwant Singh Raghuwansh Bedi Krishna Hanmantrao Belgaumkar, Daniel Bevan, M D Billington Mohammed Sarfraz Husain Bokhari, N R M Buist, G W Chance, T L Conradie, Purushottam Ramkrishna Dange, A J Dell, H R de Souza, B L Dodson, Gulamabbas Juma Ebrahim, Sundari Ebrahim, Davina C Embleton, Eileen Evans, A C Fairburn, S G A Forsyth Valentine I French A W Galbraith Prakash Chandra Garg, Laxmidas Liladhar Ghelani K D Gill, B L. Griffiths, Jagmohan Grover, Indira Gupta, V C Harrison William Hazeldine, H J Houston, Yujen Edward Hsia E H Innes, Kunjamma Itty, Jacob Jacobson, Patricia H M Jones Att Ketusincha, Dhanapati Laha Philip Lanzkowsky, Stephen Leung Wing Chiu A R. Levin, S R McKay, Sabnavis Madhava Rau, H J Marrable Anila Mehta, R E Midwinter Janette Millar, J D Miller, D J Moorhouse, Peter Morris, Yousuff Motala Humayun Mumtaz Husain, M F Nasser, A D Noble, Lilay Abdulla Nouri, Bridget O Connell Marjory E Plumb Elizabeth J Porter, Rajeshwar Prasad, Sheila G Quain, Venkata S Rajagopalan, Anantanarayana Ramasubramanian, Susan E M Richards A P Roberts, Jagannath Roy, Ananada Kali Sain, J V Sawdy, Theresa Sebestyen, Rathindra Nath Sen, D C B Senaratne, Saida Siddiqi, D J Sills P H Sive, G J A I Snodgrass, S D Stephen, Shesh Raj Suxena Dinar Talati, Predyot Kumar Taludkar, E V Tetteh Lartey Patricia M S Vaughan, Purushottam Lal Verma, Cecilia C Ward Gillian M Watkins H A D Weerasooriya, R. E Wild J H Williams, G B Winter, Julia M Winter, H O Wooller, Ma Sein Yee, Janet C J Young, Ka Man Carmen Yuen, Zafar Hussain Zaidi

Wellcome Trust

Prof John McMichael has been appointed a trustee of the Wellcome Trust in place of Sir Henry Dale, who retired from the trusteeship in July and was succeeded as chairman by Lord Piercy Sir Henry Dale will continue to serve the Trust in an advisory capacity as scientific consultant

Gairdner Foundation

This Canadian foundation has made awards to Prof J H Burn (Oxford), Prof John McMichael (London), Prof J H Gibbon, Jr (Philadelphia), Prof W F Hamilton (Augusta), Dr K Meyer (New York), and Prof A R Rich (Baltimore)

Professor Burn, who formerly held the chair of pharmacology at Oxford University, receives his award for outstanding contributions to knowledge of the action of drugs in cardiovascular disease

The citation for Professor McMichael speaks not only of his place as one of the pioneers of cardiac catheterisation but also of his earlier work on the liver circulation and on the lungs, as well as his studies with many collaborators on heart-failure, and his recent work on malignant hypertension The citation concludes "One of his greatest contributions, less tangible but possibly more significant than any discrete discovery, has been the introduction of clinical physiology to a generation of physicians in Britain and the Commonwealth"

The Gairdner Foundation was incorporated in 1957, and its funds are derived from personal gifts of Mr J A Gairdner and his family The awards, of $5000 each, are prizes for achievement and not grants for future research Last year's award winners were Dr Alfred Blalock and Dr Helen Taussig (Baltimore), Dr Harry Rose and Dr Charles Rogan (New York), Prof W D M Paton (Oxford), Prof Eleanor Zaimis (London), and Dr W G Bigelow (Toronto)

King Edward Medical College, Lahore

The first centenary of this college will be celebrated in Lahore by a three-day meeting which will be opened on Nov 16 by the President of Pakistan A series of lectures and a clinicopathological conference is to be held, and the centenary oration will be delivered by Lieut-Colonel S M K Mallick, dean of the faculty of medicine, University of Punjab

Those who have been associated with this college and wish to obtain further information may write to Mr M Ismet Anwar, F R C S, secretary, centenary committee, King Edward Medical College, Lahore, Pakistan, or to Lieut-Colonel Fahim A Khan, medical adviser to the High Commissioner for Pakistan in the U K, 35, Lowndes Square, London, S W 1

A Midwife's Training

The General Nursing Council and Central Midwives Board have agreed in principle that the general training of women student nurses should include three months' obstetric training which will entitle them to a reduction of two months if they take a course in midwifery The Board intend ultimately to organise a single period of ten months' training leading to the midwife's certificate, but for the immediate future a four-months first period will be organised for general-trained nurses who take the approved course of obstetric training These changes will require a new statutory instrument before they can be introduced

Westminster Hospital Dinner

The Westminster Hospital old students dinner was held on Oct 13

Dr J A Gorsky, the chairman, said that medicine had become over-compartmentalised At the boundaries between specialties there was acrimonious controversy, and the divisions, originally made for ease of teaching, were now having a disintegrative effect General practitioners were isolated in a regime in which Civil Servants were no longer servants but masters It was now impossible for a family doctor to become a consultant, and yet many famous doctors in the past had followed this path He felt that many general practitioners lacked the adaptability at present necessary They were unable or unwilling to change their ideas, and maintained a mental attitude which would have been more appropriate half a century ago Sir Stanford Cade, proposing The Chairman, told of Dr Gorsky s devoted service over forty years in his general practice, and of his wide range of interests This was the first time a general practitioner had taken the chair Among the guests he welcomed by name were the matron, Miss Lavinia Young who was present for the first time, and Sir Alexander Fleck, former chairman of Imperial Chemical Industries, who had just been appointed chairman of the medical school council Dr Donald Teare replied for the guests

In the afternoon clinical demonstrations and ward rounds had been arranged for the old students

London Hospital Dinner

Mr Victor Lack presided at the old students' dinner on Oct 13

Reviewing the two years since the last dinner, Dr H B May, dean of the medical college, spoke of a tremendous amount of building The east wing of the hospital had been rebuilt, and a cross wing was going up, across the garden The college, with its new hall, gymnasium, and study bedrooms, could have 150 people in residence what was needed now was a new building for the students' union As chairman of the hospital Sir John Mann had been succeeded by Mr Harry Moore In the two years the clinical staff had lost by retirement Mr Lack, Dr M H Jupe, Mr Alan Perry, Dr Kenneth Tallerman, and new appointments included those of Dr Anthony Jackson, Mr A G Parks, Dr Betty Evans, Dr A Stuart Mason, and Dr M A Floyer Prof I Doniach had succeeded Prof Dorothy Russell, who had been a tower of strength and inspiration since she came to the hospital in 1919, and the place of Prof J L D'Silva, now professor of physiology at King's College, had been taken by Prof K W Cross from St Mary's Among old Londoners, Dr George Godber was to be chief medical officer of the Ministry of Health from Dec 1 As for the 32 clubs of the clubs' union, their activities were multifarious, but the rugby xv had been only narrowly defeated by St Thomas's in the final for the interhospital cup Dr May concluded that the place was still the same " Buildings don't matter a great deal What does matter is the quality of our society "

Proposing The Chairman, Mr Alan Brews spoke of his vice-presidency of the Royal College of Obstetricians and Gynæcologists Messages were read from Sir Eardley Holland and from Mr Arthur Bell, the president, while Sir Andrew Claye, immediate past president, was present at the dinner As a student at The London, Victor Lack had been described as of " very modest application " he believed in a general education and a lot of his time had to be devoted to racing motoring at Brooklands But his toughness, physical and mental, was combined with sympathy, so that he bore down with his patients in labour He had left an indelible mark on his hospital, being remembered as a conservative obstetrician, a very quick and deft (and above all very safe) surgeon, and an able and wise administrator

Responding, Mr Lack summed up the tradition of the hospital as kindness and care of the patient So long as that tradition lasted, The London would continue to turn out happy, kindly, and sometimes even skilful doctors

A notable feature of the dinner was the presence of three medical generations of the Grogono family Dr Eric W Grogono, who qualified from The London in 1902, sat on the chairman's right, while his grandson, an obstetric resident, was at a less inhibited table

General Practitioner Research Group

This group, which was formed to undertake clinical trials in general practice (*Practitioner*, 1960, 184, 500), has recently been awarded a research grant by the National Institutes of Health, U S Public Health Service The grant, amounting to $5000 a year, is for two years, and is to be used for the " investigation of the value of various tranquillising and other psychotherapeutic drugs in general practice " Any general practitioner who might be interested in taking part in this investigation is asked to communicate with the director of the group, Dr David Wheatley, 270, Staines Road, Twickenham

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On Oct 3 Sir Harry Platt gave the Edward Holman Skinner lecture before the Kansas City Southwest Clinical Society His subject was Whither Medicine?

At the London School of Hygiene and Tropical Medicine, the Barnard Room in the library has been dedicated by Sir Philip Manson-Bahr in memory of Cyril Cuthbert Barnard, librarian of the school from 1921 to 1959

CORRIGENDUM *Nature of Essential Hypertension*—In the article by Dr Morrison and Professor Morris (Oct 15, p 829) the keys to figs 2 and 3 were wrongly placed In fig 2 the continuous lines are regression lines at low pressure levels, and the interrupted lines regression lines at high pressure levels In fig 3 the continuous lines refer to relatives of normotensive subjects, the interrupted lines to relatives of middle-aged hypertensive subjects (Hamilton et al 1954b), and the interrupted lines with circles to relatives of middle-aged hypertensive subjects (Sobye 1948)

Diary of the Week

OCT 23 TO 29

Monday, 24th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 30 P M *Odontology* Prof R V Bradlaw E tenebris (Presidential address)
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
4 P M Dr John Vallance-Owen Insulin Activity and Antagonism in Plasma

Tuesday, 25th

ROYAL SOCIETY OF MEDICINE
8 P M *Medicine* Dr A A G Lewis, Dr A G Spencer, Dr Stanley Shaldon Diuretics
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr C H Andrewes Common Cold
ST MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W 2
5 P M Sir Wilfrid Le Gros Clark Synthesis of Anatomy and Physiology in Neurological Studies
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Dr E H Larkin Drug Treatment in Psychiatry
ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P M Prof Ian Aird Blood groups and Disease
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W 1
5 P M Prof R A Kehoe (University of Cincinnati) "Normal Metabolism of Lead (First Harben lecture)
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr Brian Russell Bacteria on the Surface of the Skin
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) Dr D J Williams Epileptic Patients a Century Ago (University lecture)
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Mr H J Seddon Peripheral Nerve Injuries

Wednesday, 26th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W C 2
5 P M Mr D M Wallace Carcinoma of the Bladder
5 P M Dr D H Tompsett Injection of the Blood Vessels of the Heart with Synthetic Resin (Arnott demonstration)
ROYAL SOCIETY OF MEDICINE
5 P M *Endocrinology* Prof H L Sheehan Atypical Hypopituitarism (Presidential address)
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr J H Wilkinson Biochemistry of the Thyroid
ROYAL FREE HOSPITAL, Gray's Inn Road, W C 1
5 15 P M Dr Ian Mackay (Melbourne) Lupoid Hepatitis
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5 P M Professor Kehoe Metabolism of Lead under "Abnormal" Conditions (*Second Harben lecture*)
INSTITUTE OF DERMATOLOGY
5 30 P M Dr R W Riddell Ringworm Fungi
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Mr O S Tubbs Cardiac Surgery in the Older Age-group
UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Dr R R Macdonald Cervical mucus, twins
6 P M Mr D W Currie Anatomy of the Pelvic Floor and Prolapse "
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, 9, Queen Steet, Edinburgh,
5 P M Sir Stanley Davidson Anæmia and Operations on the Gastro-intestinal Tract (Sydney Watson Smith lecture)

Thursday, 27th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Dr Cuthbert Dukes Genetics in Relation to Surgery (Thomas Vicary lecture)
ROYAL SOCIETY OF MEDICINE
8 P M *Urology* Mr M F Nicholls Cancer, Palliation or Cure? (Presidential address)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Prof. Wilson Smith Virus Flocculation Reactions
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5 P M Professor Kehoe Present Hygienic Problems Relating to the Absorption of Lead (Last Harben lecture)
INSTITUTE OF DERMATOLOGY
5 30 P M Dr C D Calnan *Itching, Physiological and Pathological*
UNIVERSITY OF ST ANDREWS
5 P M (Physiology department, Queen's College, Dundee) Dr R S F Schilling Recent Studies of Chronic Respiratory Disease in Textile Workers

Friday, 28th

ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS, 27, Sussex Place, Regent's Park, N W 1
5 P M Mr Ian MacGillivray Hypertension in Pregnancy and its Consequences (William Blair-Bell lecture)
ROYAL SOCIETY OF MEDICINE
8 15 P M *Obstetrics and Gynæcology* Mr W R Winterton London Gynæcological Hospitals (Presidential address)
POSTGRADUATE MEDICAL SCHOOL
10 A M Mr G E Mavor Aspects of Arterial Grafting in Atherosclerosis of the Lower Limb Arteries
4 P M Dr G de J Lee Pulmonary Vascular Homœostasis in Man.
INSTITUTE OF DENTAL SURGERY, Gray's Inn Road, W C 1
4 30 P M Lord Cohen of Birkenhead Diagnostic Significance of Pain (Wilkinson lecture)
ASSOCIATION OF INDUSTRIAL MEDICAL OFFICERS
10 A M (Royal College of Surgeons, Lincoln's Inn Fields, W C 2) Dr H B Austin Organisation of a Small Factory Medical Service by a General Practitioner (Opening of two-day meeting.)

Saturday, 29th

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
11 15 A M (Hammersmith Hospital, Ducane Road, W 12) Prof Ian Donald Modern Diagnostic Aids in Obstetrics

The Lancet · Saturday 29 October 1960

THE TREATMENT OF OBESITY BY THE "HIGH-FAT" DIET

THE INEVITABILITY OF CALORIES

John Yudkin
M.A., M.D , Ph.D Cantab , M.R.C.P , F.R.I C
PROFESSOR OF NUTRITION IN THE UNIVERSITY OF LONDON
AT QUEEN ELIZABETH COLLEGE, LONDON, W 8

Margaret Carey
B Sc. Lond
CHIEF DIETITIAN, ST GEORGE'S HOSPITAL, LONDON, W 1

The difficulties in treating obesity lie not so much in that we do not know what to do, but that we do not know very well how to do it What we have to do is to persuade the patient to eat less, it is in this that we often fail One of the causes of failure is that the conventional low-calorie diets, restricted in both fat and carbohydrate, usually lead to hunger which the patient is unable, or unwilling, to tolerate

In the last few years, many have found that diets restricted in carbohydrate only, and not in fat, give satisfactory weight-reduction without hunger (e g , Yudkin 1958) Since these diets allow unlimited protein and fat, they are sometimes referred to as high-fat diets rather than low-carbohydrate diets Understandably, the phrase "high-fat" in relation to weight-reduction is sufficiently startling to have made a deep impression both on the public and on the medical profession (see for example correspondence in the *British Medical Journal* in early 1959) Superficially, it appears that a diet which makes an obese person lose weight whilst allowing him unlimited fat refutes the orthodox contention that weight-loss can only be achieved by caloric restriction. This refutation of the orthodox rests on the idea put forward by Pennington (1953a) that obese people gained weight because of a metabolic defect. They were said to be unable to metabolise carbohydrate completely, so that it was oxidised only as far as pyruvic acid This was supposed to inhibit fat oxidation and stimulate fat synthesis Severe restriction of dietary carbohydrate would lead to mobilisation of body-fat, even in the presence of large amounts of dietary fat.

Later reports by Kekwick and Pawan (1953, 1956) were taken by many to support this view These authors gave obese patients diets of 1000 calories, in which 90% of the calories came either from protein, or from fat, or from carbohydrate During the 8 or 10 days in which the patients ate the diets, they lost most weight with the fat diet, and lost little or none, or even gained it, with the carbohydrate diet. Kekwick and Pawan (1956) suggested that "obese patients must alter their metabolism in response to the contents of the diet"

These conclusions, however, are unlikely, and extrapolation from them (e g , by Mackarness 1958) unwarranted As long ago as 1932, Lyon and Dunlop had obtained similar results and, quite reasonably, explained them as being due to variation in loss or retention of fluid. The results of Kekwick and Pawan were obtained on patients given the various diets for only a few days It was clearly necessary to repeat these experiments for longer periods This was done by Pilkington and his colleagues (1960), who studied the effect of similar diets for periods of 18 or 24 days Although the first few days on each diet gave the same sort of results as those of Kekwick and Pawan, there was after this a steady rate of weight-loss, which was the same with each diet They concluded that temporary differences with the different diets were due mainly to changes in fluid-balance Olesen and Quaade (1960) reached the same conclusions

It seems then fairly certain that, apart from these initial differences, a calorically restricted diet leads to weight-loss in the obese which is independent of the source of calories This makes it unlikely that the "high-fat" diet recommended for the treatment of obesity owes its effectiveness to some peculiarity in metabolism

The alternative explanation is that the "high-fat" diet leads to weight-loss because, in spite of its unrestricted allowance of fat and protein, it is in fact a low-calorie diet This was the explanation that one of us had already put forward (Yudkin 1958) Such a view is simple and orthodox, and therefore unspectacular This is probably one of the reasons why many have preferred to accept the more exciting theories based on some postulated but unproven defect in metabolism Yudkin (1958) pointed out that a diet severely restricted in carbohydrate would, if anything, also be somewhat reduced in fat. Thus, restriction of bread is likely to lead to a lower intake of butter Restriction of ice-cream, cakes, and most biscuits restricts not only the carbohydrate they contain but also the fat.

These considerations, however, are still theoretical. Pennington (1953b) stated that his subjects lost weight on low-carbohydrate diets containing 3000 calories or more, but gave no indication of their previous diet, or quantitative details of their low-carbohydrate diet The experiments we describe were undertaken to ascertain the effect of a restriction of carbohydrate on the intake of calories, fat, and protein.

The Investigation

We have studied six adult subjects Four were nursing sisters, and the other two were the father and brother of one of them Apart from their overweight, all were apparently healthy and were working during the time of the investigation They were carefully instructed by one of us in the weighing and recording of their complete diets They were told to eat their usual foods for 2 weeks At the end of this time, they were asked to reduce the carbohydrate in their diets to about 50 g daily for a further 2 weeks, and to eat as much protein and fat as they liked. They were given a list of foods containing carbohydrate in significant amounts, and told that they could eat unlimited amounts of such foods as meat, fish, eggs, cheese, butter, margarine, and cream. They were not asked to restrict water or salt. They weighed themselves daily, at the same time, throughout the 4 weeks of the test.

From the daily dietary records, we calculated the intake of calories, protein, fat, and carbohydrate As far as possible, we used the tables of McCance and Widdowson (1946), for some proprietary foods, we obtained analytical figures from the manufacturers

TABLE I—EFFECT OF "HIGH-FAT" DIET ON INTAKE OF CALORIES
AVERAGE DAILY INTAKE OVER TWO WEEKS

Subject	Height (ft in)	Weight (lb)	Weight loss (lb)	Daily caloric intake	
				"Normal"	"High-fat"
1 (M)	5 11½	189	9	3150	1550
2 (M)	5 9	215	8	2900	1600
3 (F)	5 6½	149½	6	2600	1350
4 (F)	5 2	169	5	2000	1250
5 (F)	5 3	167	6½	1600	1250
6 (F)	5 4½	142*	2†	1500	1300

* After loss of 3 lb during 2 weeks on normal diet
† Loss in 12 days on "high-fat" diet

Results

In all subjects the caloric intake fell significantly during the time they were eating the low-carbohydrate diet (table I) The reduction in calories ranged from 200 to 1900 a day, or from 13% to 55% of the original calories These changes were all statistically significant at the 5% level, or better

During the initial 2 weeks, five of the subjects did not change weight by more than 1 lb Subject no 6 lost 3 lb, and was clearly restricting her intake of food during this preliminary period In the next 2 weeks, on the carbohydrate-restricted diet, all the subjects lost weight Subject no 6 kept records for only 12 days in this period, during which she lost another 2 lb The other subjects lost from 5 lb to 9 lb in 14 days The loss in weight was, with only one exception, proportional to the decrease in calories

In spite of the loss of weight, and in spite of the reduction in calories—in some instances considerable—none of the subjects complained of hunger, though two reported an urge to eat foods containing sugar or starch This is in line with our previous experience with more than a hundred subjects (Yudkin 1959) The implications of this observation are discussed later

All the subjects substantially reduced their intake of carbohydrate, as they were requested to do (table II) With their normal diets, they had consumed between about 140 g and 500 g carbohydrate as a daily average, on a carbohydrate-restricted diet, they reduced these amounts to between 30 g and 55 g

In five subjects, the protein intake was not affected by the changed diet The exception was subject no 6, who had been eating a restricted diet during the preliminary 2 weeks When told to restrict carbohydrate and eat as much fat and protein as she wished, she ate significantly more protein than before—a daily average of 72 g compared with 57 g

None of the six subjects showed a significant increase in the amount of fat consumed Three of them in fact showed a significant reduction of fat, varying from 22 g to 35 g daily

Discussion

We have assessed dietary intake by records of the subjects' weighing of their food, and the conversion of this into terms of nutrients from the food tables There are several ways in which this method may be inaccurate (Chappell 1955) However, each subject was weighing his diet himself both during the preliminary period and during the experimental period Since we were interested mainly in the changes in dietary intake between these two periods, many of the possible sources of absolute error in the methods we have used will be similar in both periods and so may be ignored One source of error, however, is inherent in any investigation of this sort, and that is the change of the diet by the subject himself because he is under observation This probably accounts for the low caloric intake of subject no 6 during the preliminary period That she lost weight during this time makes it certain that she normally ate more than this It is likely that her normal diet consisted simply of more food, and so contained more protein, fat, and carbohydrate

The main purpose of this investigation was to find out what happened to the intake of calories, and of protein and fat, in diets considerably restricted in carbohydrate The answer seems unequivocal, there was a reduction in calories, no significant change in protein, and either no significant change, or else a reduction, in fat

These results show that the term "high-fat diet" is a misnomer, the correct term is "low-carbohydrate diet" We now also understand why this diet can lead to loss of weight in the obese It is low in calories, and it is this which causes loss of weight, and not some peculiarity in carbohydrate metabolism Nevertheless, the origin of the term "high-fat diet" is understandable Firstly, orthodox diets for weight-reduction restrict fat, but the low-carbohydrate diet allows unrestricted fat Secondly, since the total intake of calories is restricted, the *proportion* coming from fat is usually increased Thirdly, and most important, the term "high-fat" derives from the confusion between "unrestricted" and "unlimited" Attention has already been drawn to this (Yudkin 1959), when it was pointed out that "as much as you like" means only what it says It means as much as a person wants to take, and not vast and unlimited amounts As we see, in diets with restricted carbohydrate,

TABLE II—EFFECT OF "HIGH-FAT" DIET ON INTAKE OF PROTEIN, FAT, CARBOHYDRATE, AND CALORIES
AVERAGE DAILY INTAKE IN GRAMMES, ± STANDARD DEVIATION

Subject	Diet	Calories		Carbohydrate		Protein		Fat	
		±S D	Difference and significance	g ±S D	Difference and significance	g ±S D	Difference and significance	g ±S D	Difference and significance
1	Normal High fat	3460±547 1510±331	−1920c	495±114 43± 7 5	−425c	106±17 7 100±21 9	−6 N S	126±29 2 104±26 6	−22a
2	Normal High-fat	2900±441 1620±319	−1280c	345±63 2 55±10 7	−290c	95±16 8 105±20 9	+10 N S	131±29 2 106±22 8	−25a
3	Normal High-fat	2580±304 1340±259	−1240c	285±58 0 49± 8 3	−236c	78±14 3 75±16 7	−3 N S	127±16 2 92±17 4	−35c
4	Normal High-fat	1990±427 1260±213	−730c	212±62·4 30± 6 5	−182c	67±10 0 70±11 8	+3 N S	99±23 0 92±18 1	−7 N.S.
5	Normal High-fat	1610±308 1270±274	−340c	156±35 9 43±12 7	−113c	58±10 5 59±11 4	+1 N S	85±22 4 91±25 5	+6 N S
6	Normal High-fat	1480±301 1300±175	−180a	138±39 1 42± 6 1	−96c	57±14 5 72±18 0	+15a	78±21 4 92±21 0	+14 N.S

Significance N S, not significant, a, P<0 05, c, P<0 001 "as much as you like" of fat turns out to be no more fat than before, and sometimes even less.

In our subjects, the carbohydrate intake was reduced considerably. We do not know whether all obese subjects need such drastic reduction in order to lose weight. It should, however, be noted that half a pint of milk and reasonable helpings of green vegetables will give some 25 g. or 30 g. of carbohydrate. In order to keep carbohydrate intake at a low level, it is important that the patient be told that glucose or sorbitol should not be taken as alternatives for sugar. He should be told also that bread substitutes, in spite of the claims made for them, do not necessarily contain a significantly lower amount of carbohydrate than bread. In this connection, we have had some analyses made of the commoner bread substitutes, and have found that most of those consumed by the obese give them (besides a feeling of self-righteousness) a great deal of carbohydrate.

The results we have reported raise a problem in relation to control of appetite, at least in the obese. Current theories assume that appetite is controlled chiefly, if not entirely, by calories; explicitly or implicitly they give equal values to calories from protein, fat, and carbohydrate. Yet we have seen that a change to a low-carbohydrate diet may in the obese reduce calories to half or less, but may not lead to hunger. So long as it was thought that the diet was high in fat, it might have been postulated that this was responsible for the satiety (*Lancet* 1960). But the diet is not high in fat, contains significantly fewer calories, and is nevertheless satiating. We can appreciate this surprising fact—and, perhaps, derive a clue towards explaining it—if we consider the situation in reverse. An obese person is consuming a low-carbohydrate diet which gives him, say, 2000 calories, derived mostly from protein and fat. On this diet he is quite satisfied. He now adds an amount of carbohydrate which gives him 1000 or so additional calories. If his appetite were controlled entirely by calories, he would consume less of the other foods to the extent of the same 1000 calories. But he does not do this; in fact, he is likely, in addition to his 1000 extra calories from carbohydrate, to take more fat as well.

It would seem from this that carbohydrate does not satisfy the appetite; it may even increase it, because more dietary carbohydrate may lead to more dietary fat. This conclusion is supported by the observation that the addition of glucose to a reducing diet led to a decreased loss of weight; this could not be accounted for by the calories from the glucose, and suggests that the glucose stimulated the appetite (Yudkin 1959).

These considerations are derived from a restricted study with obese subjects. We wish to stress that the conclusions which can be drawn from them must at present also be restricted.

Firstly, there is presumably a limit to the amount of carbohydrate which one can eat without reaching satiety. It is likely that this limit varies with different individuals, and it may be that the varying extent of "excessive" consumption in our six subjects is an indication of the variation in the satiety value of carbohydrate for different individuals.

Secondly, we do not know whether these conclusions apply only to obese persons. If they do, it is possible to imagine that this signifies a major and qualitative difference between the obese and the non-obese; the obese may be those in whom carbohydrate does not easily satisfy the appetite. This is similar to the suggestion made by Beaudoin et al. (1953). On the other hand, if this property of carbohydrate is common to all people, though perhaps in varying degrees, it should be possible to make thin people put on weight by increasing dietary carbohydrate. Ordinary dietary recommendations, which usually involve an increase in foods such as butter and cream, are often notoriously ineffective in increasing the weight of thin people.

Thirdly, we have spoken of carbohydrate as if all forms behave in the same way. For this, we have no evidence. It may well be, for example, that sugars, which are rapidly absorbed, behave differently from starches. This, and the other questions raised in this discussion, cannot be answered without further investigation.

Summary

A study has been made of the intake of calories, protein, fat, and carbohydrate of six obese subjects before and during the consumption of a "high-fat" diet. For this diet, the subjects were instructed to limit only carbohydrate, and to consume as much fat and protein as they wished. All subjects lost weight during the 2 weeks on the diet. Their daily intake of calories was found to be from 200 to 1900 lower, a reduction of between 13% and 55%. No subject consumed significantly more fat than before; three subjects consumed significantly less.

Thus, the term "high-fat" diet is wrong; it should be "low-carbohydrate" diet. The obese patient loses weight on this diet, not because of some peculiar metabolism of fat but because of a reduction in calories. The implications of these findings are discussed in relation to theories of appetite control.

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ABSORPTION, EXCRETION, AND RETENTION OF STRONTIUM BY BREAST-FED AND BOTTLE-FED BABIES

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THE amount of strontium in the bones of newborn babies has been studied in recent years, and analyses of bones of older babies, of children, and of adults have also been made (Bryant et al. 1958, Thurber et al. 1958, Bryant et al. 1959). The average ratio of strontium, measured in microgrammes, to calcium, measured in milligrammes,

$$\text{i.e., } \frac{\text{strontium} \times 10^3}{\text{calcium}}$$

in the bones of British babies was found to be about 0.19 at birth, and this ratio was shown to reach the adult level of about 0.3 after 18 years (Bryant et al. 1958). At all ages, however, the results were somewhat variable, depending no doubt partly upon the amount of strontium in the food Values for bones of individual babies during the first 6 months were sometimes higher or sometimes lower than the average at birth, and the evidence is insufficient to say whether a rise occurs in the suckling period There is no doubt, however, that babies are born with strontium in their skeletons, and if Widdowson and Spray's (1951) figure of 28 g is taken for the average amount of calcium in the body of a fullterm baby at birth, then the amount of strontium must be just over 5 mg

There is evidence to show that the adult body discriminates against strontium in favour of calcium (Harrison et al 1955, Comar et al 1957, Laszlo and Spencer 1958) It has been demonstrated that the ratio of strontium to calcium absorbed from the intestine is always lower than the ratio in the diet, and further, the ratio of strontium to calcium excreted in the urine is higher than the ratio in the plasma or in the bones, and presumably higher therefore than the ratio in the body as a whole The metabolism of strontium in children between 4 and 14 years has recently been studied (Bedford, Harrison, Raymond and Sutton 1960), and it appears that by the age of 14 the relation between the turnover of strontium and calcium is similar to that in adult life

Cow's milk contains about six times as much strontium as human milk, but no previous studies have been made of how the strontium of milk is metabolised The present investigation concerns week-old babies who were having only breast milk or only a cow's milk preparation We originally hoped to make determinations of strontium-90, but, because the total amount of urine and fæces passed by a baby in the experimental period contained insufficient strontium-90 for one determination, the study was of necessity limited to the stable element

Subjects and Methods

Nine breast-fed and nine bottle-fed baby boys were studied in the main investigation They were all born at the Maternity Hospital, Mill Road, Cambridge The days chosen for study were the 6th, 7th, and 8th after birth, by which time the flow of breast milk was established Only those babies who had been and still were fully breast-fed were included in the first group The others had had nothing but a cow's milk preparation since birth The breast-fed babies, whose average weight during the study was 3 4 kg, were weighed accurately *before and after each of the fifteen feeds* during the 3 days, and their intake of milk was obtained by difference Milk was collected from each mother and analysed, and samples were taken from fifteen other mothers as well to gain more information about the amount of strontium in breast milk

The bottle-fed babies, whose average weight was 3 6 kg, received a preparation made from dried whole cow's milk and lactose A special batch was made for us by the manufacturers, and this was used for the first six babies We then found that the commercial cow's milk preparation in general use at the hospital contained twice as much stable strontium as the special preparation, and this was used for the three babies studied during the latter part of the investigation

For all the bottle-fed babies an amount of milk powder sufficient for one day was accurately weighed out and mixed with a measured volume of distilled water The mixture was stored in a refrigerator, and portions were transferred to the feeding bottle as required, the bottle was weighed before and after each feed

The methods used for collecting quantitatively all urine and fæces passed by the babies, and their regurgitated food, have been described by Slater (1961) A carmine marker was given (0 25 g mixed with a little water in a feeding bottle) before the first feed of the 3-day period and before the first feed on the 4th day Fæces were collected from the first to the second appearance of the marker

Portions of the food, urine, fæces, and regurgitated food were dried and ashed at 450°C, the ash was extracted with HCl, and determinations of strontium, calcium, and phosphorus were made on the extract

TABLE I—STRONTIUM (μG PER 100 ML) AND CALCIUM AND PHOSPHORUS (*MG PER 100 ML*) *IN BREAST MILK AND THE TWO COW'S MILK* PREPARATIONS

Type of milk	Sr	Ca	P
Breast milk			
Average for mothers whose babies were studied	6 9	27 8	15 6
Pooled sample from 15 other mothers	8 7	24 6	15 5
Cow's milk preparation diluted with water			
Analysed as fed to babies			
Special preparation	26 2	102	76
Commercial preparation	52 5	102	76

Calcium was determined by the Clark and Collip modification of the Kramer and Tisdall method, as described by Economou-Mavrou and McCance (1958), and phosphorus was determined as described by Fiske and Subbarow (1925), after heating a sample of the acid extract of the ash with a few drops of concentrated H_2SO_4 to ensure that all the phosphorus was present as orthophosphate Strontium was separated as described by Harrison (1958), and determined either by neutron activation (Harrison and Raymond 1955) or by means of a 'Unicam' flame spectrophotometer, using the additive standard method (Harrison 1958)

"Blank" determinations were made on washings from the equipment used to collect the excreta, to ensure that the strontium measured had come from the baby and not from any extraneous source The amount of strontium in these washings was negligible

Results

Table I shows the average composition of breast milk from the mothers whose babies were included in this investigation, and of a pooled sample of milk from fifteen mothers at the same stage of lactation The composition of the two samples of the cow's milk preparation, diluted as they were fed to the babies, is also given The special cow's milk preparation contained about four times, and the commercial preparation eight times, as

TABLE II—INTAKES, EXCRETIONS, ABSORPTIONS, AND RETENTIONS OF STRONTIUM, CALCIUM, AND PHOSPHORUS BY BREAST-FED AND BOTTLE-FED BABIES

Mean values Standard errors in parentheses

—	Intake	Output			"Absorption"	"Retention"
		Urine	Fæces	Total		
Strontium (μg per kg per 24 hr)						
Breast-fed babies	8 (±0 5)	14 (±2 6)	14 (±2 0)	28 (±3 0)	−6 (±1 9)	−20 (±2 9)
Bottle-fed babies						
Special cow's milk preparation	35 (±1 3)	2 (±0 6)	24 (±2 9)	26 (±2 7)	+11 (±2 7)	+9 (±1 9)
Commercial cow s milk preparation	72 (±2 2)	2 (±0 5)	19 (±1 5)	21 (±1 7)	+53 (±3 2)	+51 (±3·0)
Calcium (mg per kg per 24 hr)						
Breast-fed babies	35 7 (±4 1)	5 3 (±0 8)	15 4 (±1 9)	20 7 (±2 1)	20 3 (±3 3)	15 0 (±2 7)
Bottle-fed babies	135 (±4 3)	2 4 (±1 2)	52 8 (±4 6)	55 2 (±4 5)	82 2 (±4 6)	79 8 (±4 7)
Phosphorus (mg per kg per 24 hr)						
Breast-fed babies	19 5 (±1 6)	0 5 (±0 1)	2 2 (±0 3)	2 7 (±0 3)	17 3 (±1 5)	16 8 (±1 5)
Bottle-fed babies	103 (±2 7)	35 2 (±2 1)	17 4 (±1 4)	52 6 (±2 4)	85 6 (±2·9)	50 4 (±3 4)

TABLE III—RELATIVE DIETARY INTAKE AND EXCRETION OF STRONTIUM AND CALCIUM

Results expressed as $\frac{Sr}{Ca} \times 10^3$

Age-group	Intake	Excretion	
		Urine	Fæces
Breast-fed babies	0 2	2 6	0 9
Bottle-fed babies			
Special cow's milk preparation	0 3	0 8	0 4
Commercial cow's milk preparation	0 5	0 8	0 5
Children aged 4–14 years (Bedford et al 1960)		1 3	1 9
Adults (Harrison et al 1955)	1 6	0 9	2 3

much strontium as the average amount in the samples of breast milk consumed by the babies in this investigation The two cow's milk preparations contained identical amounts of calcium and phosphorus, which were four times (calcium) and five times (phosphorus) as high as the concentrations in breast milk

Table II shows the mean intakes, "absorptions", excretions, and "retentions" of strontium, calcium, and phosphorus by the breast-fed and bottle-fed infants Standard errors are also given "Absorption" is calculated as the difference between the amount in the food and the fæces, and "retention" as the difference between the amount in the food and the total output in the urine and fæces together

The average strontium intakes of the bottle-fed babies having the two different cow's milk preparations were four and eight times as high as those of the babies having breast milk Despite this, the breast-fed babies excreted about seven times as much strontium in the urine The breast-fed babies excreted about the same amount of strontium in the urine as they did in the fæces, and in most cases each contained more strontium than the food These babies were therefore all in strongly negative strontium balance, although they were in positive balance for all other dietary constituents investigated, including calcium and phosphorus

All babies having the cow's milk preparations were in positive strontium balance Most of the strontium excreted was lost by way of the bowel, the urinary excretion amounting to only 7–10% of the total in contrast to 50% in the case of the breast-fed babies The infants given the commercial preparation containing the larger amount of strontium retained five times as much as the babies given the special cow's milk preparation, their urinary excretion was low and their fæcal excretion no higher than that of the other group of bottle-fed babies

The average intakes of calcium and phophorus by the babies having the special and commercial cow's milk preparations were almost identical, and, since their absorptions and excretions were also very similar, the results for the calcium and phosphorus turnover of all the bottle-fed babies have been averaged together (table II) These findings are discussed in detail elsewhere (Slater 1961), they are only given here so that the metabolism of strontium can be considered in relation to them

Table III shows the ratio of strontium × 10^3 to calcium in the food and excreta, and results previously obtained for older children and adults are given for comparison. These mean values were obtained by calculating the ratios for each individual baby and averaging them They give a measure of the body's discrimination against strontium in favour of calcium at different ages Both types of milk contained much less strontium in relation to calcium than did the adult diet, which is a reflection of the fact that calcium is preferentially secreted in milk The ratio in breast milk (0 2) was about the same as that in the baby's bones at birth In the breast-fed babies the ratio of strontium to calcium in the fæces was much higher than that in the food, which shows in another way that calcium was preferentially absorbed, or strontium preferentially secreted in the digestive juices In the bottle-fed babies having the special cow's milk preparation the fæcal ratio was also a little higher than the ratio in the food, but in the babies having the commercial preparation the ratios were almost the same

The breast-fed babies had the highest urinary strontium/calcium ratio, the bottle-fed babies excreted less strontium relative to calcium than the older children, and their value was similar to that in adults

Effect of Additional Phosphate in Breast-fed Babies

We were naturally curious to know why breast-fed babies should be removing strontium from their bones in this way, and in particular why their urinary excretion should be so much higher than that of the bottle-fed babies A possible reason seemed to be that breast milk contains so little phosphorus Breast-fed babies excrete only traces of phosphorus in the urine (Widdowson and McCance 1959, and table II), although their kidneys are capable of excreting more if the intake is raised, as it is by cow's milk

TABLE IV—URINARY EXCRETION OF STRONTIUM, CALCIUM, AND PHOSPHORUS (PER KG PER 24 HR.) BY BREAST-FED BABIES RECEIVING ADDITIONAL PHOSPHORUS

—	Strontium (µg)	Calcium (mg)	Phosphorus (mg)
Mean value	2 9	2 1	22 9
Standard error	±0 3	±0 7	±1 7

To investigate this point, eight breast-fed babies, with an average weight of 3 3 kg on the 7th day after birth, were given phosphorus, 120 mg daily as a 1 to 4 mixture of KH_2PO_4 and Na_2HPO_4, on the 5th, 6th, and 7th days after birth All the urine passed on the 7th full day after birth was collected and analysed for strontium, calcium, and phosphorus (table IV) Each of the eight babies given phosphates excreted less strontium in the urine than any of the babies getting breast milk alone, and their average excretion of strontium was nearly as low as that of the bottle-fed babies The urinary excretion of calcium was also reduced, indicating that these two chemically similar elements respond to additional phosphorus in the same way

Discussion

An unexpected result of this investigation was the high urinary excretion of strontium and calcium by the breast-fed babies, and the way in which this was reduced by the administration of phosphorus We interpret this as being an indication that the supply of phosphorus was limiting the deposition of minerals in the skeleton A second surprise was that, although the breast-fed babies were in positive calcium balance, they were in strongly negative strontium balance, and, as already stated, both urine and fæces contained more strontium than the food. The excreted strontium must have been mobilised from the bone salt laid down before birth, and two possible mechanisms might bring this about

Calcium and strontium are believed to be deposited in the skeleton in the form of hydroxyapatites and carbonates in a complex system of crystal lattices The loss of strontium from the bones could result from an exchange mechanism whereby strontium is removed from the surfaces of the crystals of bone mineral, and is replaced by calcium

Alternatively the growth and remodelling of the bone may be implicated During remodelling bone salt passes into solution, and it may be that, in the presence of a limited amount of phosphate, the calcium is preferentially redeposited along with exogenous calcium absorbed from the gut

Both these mechanisms would increase the concentration of strontium in the body fluids, and hence lead to its excretion by the kidney

McCance and Widdowson (1939), who administered strontium intravenously to themselves, found that the injected strontium was excreted slowly, and only a small fraction of it by the intestine This has been confirmed, in adults, for the stable element by Harrison et al (1955), and for strontium-85 by Fraser et al (1960) and by Bishop, Harrison, Raymond, Sutton, and Rundo (1960) It seems, however, that the intestinal glands of young babies must secrete strontium in the digestive juices in comparatively large amounts, for in eight of the nine breast-fed babies we studied the fæces contained more strontium than did the food There may also be a similar age difference in the intestinal excretion of iron (Josephs 1934, McCance and Widdowson 1937, Stearns and McKinley 1937)

If the whole skeleton of the newborn baby contains 5 mg of strontium, and if breast-fed babies continued to lose strontium at the rate observed over the short period of this investigation (20 µg per kg body-weight per day), then in less than 3 months they would have no strontium left inside them The rate of loss would no doubt decline as the amount in the body fell, but this calculation illustrates the quantities involved The bottle-fed babies having the commercial cow's milk preparation, on the other hand, would have doubled the amount of strontium in their bodies in a little over a month, they would have increased the calcium by only 17% in the same time

If the specific activity of strontium-90 is the same in the food as in the body, then, because the radioactive component will behave in the same way as the stable element as regards its absorption and excretion, these results give some indication as to what may be happening to the radioactive element The baby of today already has some strontium-90 in its bones at birth (Bryant et al 1959) During the first months of life the main source of strontium-90 for the breast-fed baby is the mother's milk If the specific activity in the baby's body is the same as, or higher than, the activity in the mother's milk, then the negative balance for stable strontium makes it unlikely that any strontium-90 will be retained so long as the baby is fully breast-fed Infants having cow's milk preparations containing more strontium-90 than breast milk probably retain a proportion of the strontium-90 along with the stable element They are therefore likely to have more strontium-90 in their bodies than breast-fed babies because (1) more is ingested, and (2) a higher proportion of the intake is probably retained

Summary

The amounts of stable strontium, calcium, and phosphorus in the food and excreta of nine breast-fed and nine bottle-fed babies were measured on the 6th, 7th, and 8th days after birth

All the breast-fed babies excreted more strontium than they ingested If the excretion had continued at the observed rate, then in about 3 months they would have had no strontium left inside them

All the babies having cow's milk preparations retained strontium, and the amount retained depended upon the amount in the milk If the retention had continued at the observed rate, then those having the commercial cow's milk preparation would have doubled the amount of strontium in their bodies in about a month

The amount of phosphorus in the diet may determine whether strontium is eliminated or retained by the body

We are grateful to Dr Douglas Gairdner for allowing us to make these measurements on the babies in his care We are also indebted to the staff at the Maternity Hospital, Mill Road, Cambridge, for their cooperation, and to Miss E Colbourn and Miss P Hennessey for their help in collecting the material Prof R A McCance first suggested phosphorus as the answer to our problem, and Dr N Hatemi made available the samples of urine from babies receiving additional phosphates, we should like to express our thanks to both of them

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NON-UNION OF UTERINE WOUNDS

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ALTHOUGH the overall incidence of rupture of the uterus has much diminished in Egypt thanks to better antenatal and intranatal care, rupture of cæsarean scars has not diminished This is mainly due to the broadening indications for cæsarean section as the operation became safer

Case-records

The following 3 cases of ruptured uterus seem worth reporting

Case 1 —A woman aged 25 years, para 2+1 and 20 weeks pregnant, was admitted to Kasr el Aini hospital as an " acute abdomen " with internal abdominal hæmorrhage She had an abdominal hysterotomy done for hyperemesis gravidarum a year before admission At laparatomy a midline perforation 7 cm long was found in the uterus A clot was filling the gap between the edges of the perforation, and the placenta was bridging the bottom of the gap The edges of the perforation were clean with no evidence of recent bruising, except in the subperitoneal layer where there was some ecchymosis After removal of the fœtus and placenta the edges of the perforation were freshened by excising a strip 3 mm thick on each side The wound in the uterus was closed in three layers and the abdomen was closed The convalescence was uneventful. Histologically the excised strips showed normal muscle/connective-tissue ratio and there was no infiltration by red cells, denoting that distruption of the wound was not recent (see figure)

Probably the wound in the uterus did not unite because of the patient's poor general condition at the time of operation Only

Section of a strip of uterine wall from the edges of the perforation in case 1 no evidence of recent bruising or laceration in the muscle-fibres.

the peritoneal layer of the uterus united and covered the gaping wound in the muscle. As the uterus became distended by the growing fœtal sac, the placenta which had been bridging the gap started to separate Bleeding then increased the intra-uterine tension so that the peritoneum gave way and the patient felt pain.

Case 2.—A married woman aged 26 years was admitted to Kasr el Aini hospital with a recurrent vesicovaginal fistula, which had appeared for the first time 7 days after a cæsarean section for contracted pelvis The fistula was repaired successfully 8 months after the operation This was followed by two abortions each at 3 months Another pregnancy ended in premature labour at 34 weeks, and a stillborn child was delivered per vaginam. The fistula recurred immediately after delivery Owing to the big size of the fistula and the fixation of tissues around it, repair was undertaken by a combined vaginal and abdominal approach. During the second abdominal stage a subperitoneal longitudinal unhealed wound occupying the lower two-thirds of the body of the uterus was noted. Dense tissue at the lower end of the wound formed the upper limit of the fistula The closure of the fistula was completed as the edges of the tear in the uterus were excised and sutured. The patient was cured She became pregnant again and was delivered by cæsarean section

This patient had a vertical lower-segment wound which was poorly united. It gave way during the subsequent vaginal delivery but the peritoneum remained intact The muscle edges of the wound did not reunite The bladder which was overlying the lower part of the incision also gave way and the fistula recurred

Case 3.—A married woman aged 28 years, para 3, was admitted for a repeat cæsarean section An elective cæsarean section was done one week before the expected date of delivery After opening the abdomen, and dividing the uterovesical peritoneum, a transverse tear 6 cm long was found in the lower uterine segment apparently at the site of the previous incision. Through the hole the membranes were bulging slightly The hole was widened and the fœtus delivered The edges of the hole were trimmed and the wound closed.

This case represents an asymptomatic rupture of a lower-segment scar and it remained asymptomatic throughout the pregnancy since vesico-uterine peritoneum was intact

Discussion

If a cæsarean section is performed for a permanent indication, such as contracted pelvis, then the decision in a subsequent pregnancy is easy cæsarean section will always be needed. But if the indication is temporary, such as antepartum hæmorrhage or prolapse of the umbilical cord, then subsequent pregnancies will cause much anxiety to the obstetrician Left to themselves, most of these mothers can safely be delivered vaginally, but in a few cases the cæsarean wound gapes during pregnancy or labour, and may not produce any symptoms or signs Thus a surgeon opening the abdomen to do a repeat section in a woman in perfectly good condition, with no pain or tenderness, is faced with a gaping wound in the uterus Such findings show that the gaping of the wound was not a sudden event, in fact cases 1 and 2 suggest that in the great majority of cæsarean scars which rupture in subsequent pregnancies, the wound edges did not unite and then gaped increasingly in later pregnancies As Pedowitz and Schwartz (1957) put it, “ most dehiscences of cæsarean wounds are conceived in the operating room and they develop during the puerperium Pregnancy only accentuates the defect”

If the placenta is bridging the defect (as in case 1) then as the defect gapes the placenta separates and hæmorrhage begins, the uterus distends and the peritoneum gives way *In these cases pain begins relatively early in pregnancy*

Another factor promoting rupture of the peritoneum is the onset of labour Here there is a great difference between lower-segment and upper-segment scars The peritoneum over the lower segment is the vesico-uterine peritoneum which is loose and thus even if the amniotic sac bulges underneath it, it does not give way Even the bladder itself may cover the defect Only during labour when the lower segment is greatly stretched and the intra-uterine pressure is much increased may the peritoneum give way Lane and Reid (1953) found in their series that when an upper-segment scar ruptures, in two-thirds of cases it does so during pregnancy and in only one-third does it manifest itself during labour On the other hand, a lower-segment scar tends to rupture only during labour

How can the obstetrician tell which patients have sound scars and which non-united or partially united ones? Among the criteria suggested have been the postoperative course, the type of cæsarean section, the skill of the operator, the type of suture material, the indication for the primary operation, the location of the placenta in the current pregnancy, and the presence of tenderness at the site of the scar

Attempts to assess directly the integrity of the scar and define its subsequent behaviour have been of two main types

(1) Routine intrauterine palpation of the previous cæsarean scar immediately after a subsequent vaginal delivery This examination can detect rupture of the scar during the vaginal delivery before shock develops Further, the integrity of the scar can be assessed and this can be a guide to the management of future pregnancies It has however, two drawbacks first, it can be performed only after taking the risk of a vaginal delivery, second, the uterine walls are so soft after labour that it may be difficult to assess the integrity of the scar

(2) Routine hysterography after cæsarean section has been tried by Baker (1955) and by Poidevin and Bockner (1958) Lateral radiographs in cases of poor union of the uterine wound show defects in the anterior wall, appearing as sacculations or deformities in the wall Patients with serious defects are advised to undergo repeat cæsarean section

I wish to thank Prof Khalil Mazhar for his kind help

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ANTIVIRAL ACTION OF INTERFERON IN EMBRYONIC CELLS

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Ho and Enders (1959) made the very interesting observation that Hela cells (a cancerous human cell-line) could be induced to make interferon, which, however, could not be assayed in Hela cells, but only in non-cancerous human cells More recently, Chany (1960) found similarly that interferon produced in KB cells (of cancerous origin) showed antiviral action in normal cells but only a weak action in KB cells It is known that interferon-treated cells show increased glycolysis (Isaacs 1960), one possible explanation for this increased glycolysis would be that interferon causes an uncoupling action on oxidative phosphorylation, thus limiting the amount of adenosine triphosphate (A T P) available for viral synthesis Indirect evidence for this suggestion comes from the observation (Isaacs, Klemperer, and Hitchcock 1960) of a number of points of resemblance between the actions of interferon and those of substances known to uncouple oxidative phosphorylation (e g, 2, 4 dinitrophenol) The lack of antiviral action of interferon in cancerous cells would then be in line with Warburg's (1956) evidence that cancerous cells can form by *anaerobic* processes all the A T P they require for growth If this line of reasoning is correct embryonic cells, which, resemble cancer cells in showing a high rate of anaerobic glycolysis (Warburg 1956), should show a similar resistance to the antiviral action of interferon during an early stage of their development,, and should later assume the behaviour characteristic of cells from adult tissues

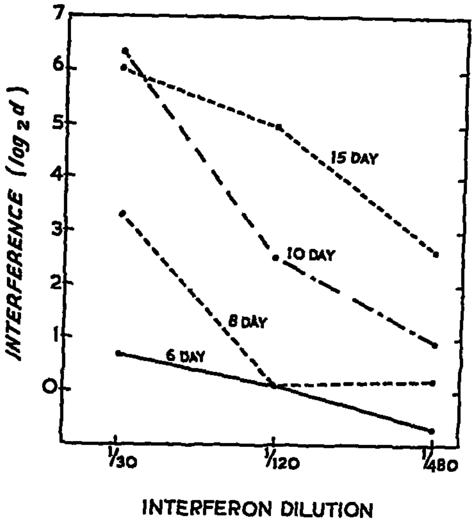
The Experiments

This possibility was investigated by testing the antiviral action of interferon on the growth of influenza virus in pieces of chorioallantoic membrane taken from chick embryos at different stages of their development

The tissues were treated with interferon in different concentrations and then infected with the PR8 strain of influenza virus After incubation in a roller-drum the virus yield was measured by the hæmagglutinin titre, and the degree of viral inhibition, or interference, is expressed as the difference between the virus yield in interferon-treated tissues and that of control tissue from embryos of the same age

It was found that the virus grew equally well in control tissues from embryos of 6, 7, 8, 10, 11, 13, or 15 days There were striking differences, however, in the sensitivity to interferon of tissues from embryos of different ages The results of one experiment (see accompanying figure) show that 15-day chorioallantoic membrane pieces are very sensitive to the action of interferon, and significant interference was found with a 1/480 dilution of the interferon preparation used On the other hand, less viral inhibition was produced by a 16-times greater concentration of the same interferon preparation in 6-day tissues The 8- and 10-day chorioallantoic membrane pieces showed intermediate sensitivity to interferon, and in this and other experiments there was a gradual, rather than a sudden, acquiring of sensitivity

Similar experiments with minced embryonic tissue from chick embroys of the same age-group and infected with the *parainfluenza 1 (Sendai)* or the NWS influenza viruses and incubated with shaking gave essentially similar results A similar result was also found in an experiment with minced embryonic tissue from mouse embryos of 7 and 18 days, in this experiment encephalomyocarditis virus and interferon prepared in mouse tissues were used.



Degree of interference produced by different amounts of interferon in tissues from chick embryos of 6, 8, 10, and 15 days

In these experiments the tissues from very young embryos resembled cancer cells in their insensitivity to interferon, but unlike cancer cells, early embryonic cells were found to produce only very low yields of interferon This was shown by comparing the yield of interferon from 6- and 11- or 13-day chorioallantoic membranes inoculated in vitro with ultraviolet irradiated influenza virus The 6-day membranes, however, are much smaller than the older membranes, and in order to compensate for these differences pieces of membrane from 6- and 11-day embryos were compared in their ability to produce both virus and interferon To do this, one group of membranes of each age-group was infected with fully infective influenza virus and the degree of virus multiplication was observed The second group was infected with ultraviolet irradiated influenza virus and the yield of interferon was measured

The table shows that the 11-day membranes produced twice as much virus but 20 times as much interferon as the 6-day membranes (The figure of 20 was obtained by finding that the 11-day interferon had to be diluted about 20 times to give the same degree of inhibition as the 6-day membranes)

Conclusions

Very young embryos therefore differ from older embryos in being much less sensitive to the antiviral action of interferon, and in producing less interferon on stimulation with ultraviolet-irradiated influenza virus We have recently found (Isaacs and Hitchcock 1960) that interferon

YIELD OF VIRUS AND INTERFERON FROM 6- AND 11-DAY EMBRYONATED TISSUES

—	Chorioallantic membranes from	
	6-day embryos	11-day embryos
(*a*) Virus yield after infection with influenza virus (log₂ hæmagglutinin titre)	6 25	7 25
(*b*) Interferon yield after inoculation with irradiated influenza virus (*log₂ d*)	*4 0*	>7 0

6-day and 11-day embryo pieces were inoculated in vitro with (*a*) influenza virus or (*b*) ultraviolet irradiated virus After 48 hours incubation at 35°C the virus yield was titrated in (*a*) and the yield of interferon in (*b*) The interferon titre is expressed as the difference between the mean log₂ yield of virus from untreated chick chorioallantoic membrane pieces and from pieces treated with the interferon preparation under test.

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may play an important role in recovery from virus infections. If these results hold true for infection of the human embryo the present results would suggest an explanation of the fact that maternal infection with rubella virus during the first 3 months of pregnancy often leads to congenital malformations (Gregg 1941, Swan 1949). Infection after the third month rarely causes congenital malformations. This could be explained by assuming that if the embryo is infected during the first third of the embryonic life, it produces very little interferon and is very insensitive to the antiviral action of interferon, just as occurs in the chick embryo. At a later stage of embryonic development it is presumed that the interferon mechanism comes into play and limits more effectively the viral infection.

These results may have wider implications. We can speculate that the antiviral action of interferon has developed in the course of evolution as an adaptive response to superficial virus infections, such as respiratory virus infections, but that the original function of interferon may have been to play a part in controlling cellular division by controlling the supply of A.T.P. During the first third of embryonic development this mechanism may not become fully established but it may play a more important role thereafter. On this view, the cancer cell is one which has escaped from the control of interferon. These speculations have the advantage that they can be subjected to experimental test.

Summary

Chorioallantoic membranes from 6-day-old chick embryos were much more resistant to the antiviral action of interferon than tissues from older embryos. Similar differences were found in whole chick and mouse embryo minced tissue, and in this respect the behaviour of early embryonic tissue resembles that of cancer cells. Unlike cancer cells, however, cells from 6-day-old chick embryos showed very weak production of interferon.

We should like to thank Mr. V. G. Law and Mrs. V. Cay-Peters for their able technical assistance.

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TWO CASES OF SARCOIDOSIS TREATED WITH MEPACRINE

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IN certain parts of Scandinavia, sarcoidosis is a major problem. Though some of its symptoms are of little consequence to the patient, it may become a distressing and even fatal affection for which satisfactory therapy is lacking. I feel justified, therefore, in reporting some observations which may indicate a new approach to treatment.

Case-reports

Case 1.—A woman, aged 51, first seen in the outpatient department in November, 1955. She complained of vague abdominal symptoms and the routine clinical examination revealed little relevant, except for a peculiar rash and moderately enlarged, firm painless lymph-nodes on both sides of the neck.

The rash consisted of groups of medium-sized, firm, brownish-red papules distributed over the face (nose, forehead and both cheeks). There were similar papules in several places on her back and on her left knee, often arranged in rings around patches of atrophic skin. This rash had been present for more than ten years and had slowly but steadily spread in spite of various forms of treatment.

The histological appearance of a biopsy specimen later proved typical of sarcoidosis, but meanwhile because of the superficial similarity of the exanthem to discoid lupus erythematosus tentative mepacrine treatment (0·1 g. three times daily) was begun. Two weeks later all the skin papules had become converted into atrophic maculæ of a peculiar brownish colour and seemed to be in full regression. The lymph-nodes were smaller but still palpable.

Mepacrine was continued, a dose of 0·1 g. twice daily being given for another fortnight and 0·1 g. daily for the following two months. During this treatment the papules were replaced by atrophic brown scars; the brown pigmentation slowly disappeared towards the end of the treatment. When the mepacrine was withdrawn, no active manifestation of sarcoidosis could be detected.

The patient did not return until August, 1958. Two new papules had then appeared on her back, but all the skin sarcoids seen in November, 1955, still seemed firmly scarred and inactive.

Case 2.—A woman, aged 30, was admitted in May, 1952, with arthralgia, erythema nodosum, and bilateral hilar lymphoma.

She returned in February, 1955, complaining of headache and impaired nasal breathing. She now had numerous enlarged painless lymph-nodes. Biopsy of a cervical node showed small crowded tuberculoid granulomas typical of sarcoidosis. The nasal mucosa both on the conchæ and on the septum showed a general, firm nodular swelling which did not respond to decongestives. The findings were said to be typical of sarcoidosis of the nasal mucosa.

During the following years there was a slow centrifugal spread of the cutaneous lesions and new lesions appeared on her right cheek and on her thighs. The nasal obstruction had become disabling. The only effective drugs were the corticosteroids which had to be administered more or less continuously from Nov. 1954 to Oct. 1958, (for most of the time, a maintenance dose of prednisone 5 mg. three times daily). Every attempt to withdraw the steroids led to an intolerable recurrence of the nasal obstruction. During the steroid treatment, the glandular and skin lesions were suppressed but did not disappear.

Mepacrine treatment was started in Oct. 1958, the dose being 0·1 g. three times daily for the first two weeks, 0·1 g. twice daily for another two weeks, and 0·1 g. daily until the end of Jan. 1959. Mepacrine was not available after this, and the treatment was continued with chloroquine in a dose of 0·25 g. daily, which the patient is still receiving.

The result was spectacular. When the patient returned after three weeks all the skin sarcoids had become tar-brown and atrophic, her nasal breathing was quite free, and the lymph-nodes had disappeared. During the following months, the cutaneous scars contracted and the brown discoloration faded. The steroid dosage (in Oct. 1958 triamcinolone 8 mg. three times daily) was slowly reduced and the drug was withdrawn in May, 1959, without there being any signs of a recurrence of the sarcoid granulomas.

Discussion

Mepacrine was introduced in 1932 as an antimalarial remedy; during the last war it was found to be a useful drug in the treatment of discoid lupus erythematosus (Prokoptchouk 1940). Since then it seems to have been abandoned for both these diseases and replaced by chloroquine and allied drugs, which probably have a similar action but are less toxic and do not give the same disagreeable pigmentation of the skin.

It is known that mepacrine is taken up preferentially by cells in the lungs, in the liver, in the spleen, and even in the kidney, and that it may be retained in the cells for a considerable time after the withdrawal of the drug

The strong brown discoloration of the cutaneous sarcoids in the present cases indicates that mepacrine may have a specific affinity for the cells of sarcoid granulomas This observation, together with their surprisingly quick disappearance, suggests that mepacrine does not act against the unknown causal agent of sarcoidosis but rather against the granuloma cells themselves The effect, in case 1 at least, seems to have been irreversible The formation of new sarcoids at a later stage in this patient indicates that the disease has not been cured

The obvious similarity between the effects of mepacrine and chloroquine in other clinical conditions suggests that chloroquine may be used instead of mepacrine in sarcoidosis Observations in some other cases of sarcoidosis, now being treated with chloroquine in this clinic, indicate that this may be true, but a definite opinion cannot yet be expressed

Summary

In two cases of generalised sarcoidosis, treatment with mepacrine resulted in strong brownish discoloration of the cutaneous sarcoids, which were converted into atrophic scars within a month In both cases other manifestations of sarcoidosis (lymph-node sarcoidosis, sarcoidosis of the nasal mucosa) disappeared together with the cutaneous sarcoids

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RESECTION OF CARCINOMA OF THE COLON IN THE PRESENCE OF OBSTRUCTION

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IMMEDIATE resection of a carcinoma of the left colon in the presence of obstruction is, in selected cases, a justifiable and safe procedure The principle underlying this procedure is that the growth, with its field of lymphatic spread, is excised, the proximal bowel is brought out as a terminal colostomy, and the distal bowel is closed over and dropped back (rather as in Hartmann's operation for carcinoma of the rectum) At a second operation—which can be postponed for an unlimited time—reconstitution of the bowel is undertaken

Case-reports

Case 1 —A man of 75 had been investigated as an outpatient and diagnosed as having a carcinoma of the lower pelvic colon Whilst waiting to come into hospital for operation he gradually became more and more obstructed, and he was finally admitted as an emergency, with absolute constipation for 5 days, which defied treatment with enemata

At laparotomy a small annular scirrhous growth was found about 3 in above the peritoneal shelf, without obvious lymph-node metastases and no local fixation Although the bowel was grossly distended the patient was thin, and radical resection of the growth was undertaken without undue difficulty The proximal end of the colon was brought out as a terminal colostomy through a gridiron incision in the left iliac fossa, and the distal end was closed with a double layer of sutures and dropped back into the pelvis 4 weeks later, at a second operation, the colon was reconstituted by dissecting out the colostomy and anastomosing it to the stump of the rectosigmoid

Case 2.—A married woman, aged 61, presented as an emergency with a history of 5 weeks' generalised colicky abdominal pain and gradually increasing constipation For the past 3 days she had had virtually no bowel action, and two enemata given the previous day had had no result She had been vomiting for 24 hours

At laparotomy, through a left paramedian incision, a carcinoma of the lower pelvic colon was found about 3 in above the peritoneal shelf The whole of the large bowel and the terminal ileum was very distended There were no obvious lymph-nodes or liver metastases Resection was performed as in the previous case, except that the terminal colostomy was fashioned at the upper end of the abdominal incision Although the patient was rather obese, no undue difficulty was experienced

Convalescence was marred by appreciable sepsis of the abdominal wound, with superficial dehiscence of most of its length This eventually cleared, and the bowel was reconstituted nearly 10 weeks later At the second operation an incisional hernia was repaired

Case 3 —A very frail thin lady of 67 was admitted to hospital as an emergency with a diagnosis of " strangulated thrombosed hæmorrhoids ", but examination revealed a prolapsed cauliflower-like carcinoma of the colon presenting outside the anus There was appreciable abdominal distension and visible peristalsis, and absolute constipation of 3 days' duration

At laparotomy, through a left paramedian incision, th intussuscepted pelvic colon was partially reduced by gentl traction until the head of the intussusceptum, with its associated carcinoma, was felt about 3 in above the pelvic floor Attempts at further reduction seemed fraught with dange and were therefore abandoned There were no obvious live metastases Although very distended the patient was extremel thin, and no trouble was experienced in resecting the growth, establishing the colostomy at the upper end of the wound, and closing off the distal stump, Closure of the abdomen was facilitated by aspiration of the colon with a sucker after it had been brought to the exterior but before actual division

Although it was explained to the patient that the colostomy was not permanent, she seemed so well satisfied that 14 months passed before she could be persuaded to submit to a second operation for colonic reconstitution This operation went smoothly, and she made an uninterrupted recovery

Case 4 —A man, aged 61, was admitted to hospital under a physician for investigation of abdominal pain, loss of weight, and diarrhœa Barium-enema studies showed an obstructive lesion at the rectosigmoid After the X-rays he became costive and rapidly obstructed, with abdominal distension and vomiting, necessitating emergency surgery

Laparotomy revealed a carcinoma just above the peritoneal shelf, together with an adherent loop of terminal ileum which was itself obstructive There were no obvious lymph-nodes or liver metastases The growth was excised together with a loop of adherent ileum, and enteroanastomosis was performed The proximal colon was brought out as a colostomy, as in the previous cases The resection necessitated mobilisation of the rectosigmoid, and the rectal stump was closed below a newly constituted peritoneal shelf

At a second operation, 9 weeks later, the colon was reconstituted This proved difficult because ectopic bone had formed in the abdominal wall, and abdominal adhesions were excessive Great difficulty was also experienced in identifying and mobilising the rectum in the hollow of the sacrum Because of prolonged ileus convalescence was slow, but the patient eventually made a good recovery, with normal defæcation and continence

Discussion

For many years surgical teaching has rightly emphasised the dangers of immediate anastomosis of large bowel in the presence of obstruction The classical procedure involves three separate operations—namely, establishment of a proximal defunctioning colostomy, resection of the diseased segment, and later closure of the colostomy A patient presenting with acute intestinal obstruction from carcinoma of the left colon will, therefore, be under surgical care for some considerable time

Before the antibiotic era the only alternative to this series of operations was the Paul-Mikulicz procedure, where the subsequent closure of the double-barrelled colostomy in an extraperitoneal fashion sometimes reduced the number of stages to two This was usually not practicable in cases of obstruction, as it did not permit a wide resection of the lymphatic field With the aid of antibiotics, intraperitoneal suturing has become far safer, but nevertheless immediate anastomosis in the presence of obstruction, and without preliminary bowel preparation, is not to be universally recommended. However, the three-stage operation can now occasionally be reduced to two by simultaneous closure of the colostomy at the same time as the major resection is undertaken Brooke (1955) advises making a colostomy as near the lesion as is practicable, so that at the second stage both the growth and the colostomy can be resected as one, and the operation can be completed by end-to-end anastomosis

Until now, except for the Paul-Mikulicz procedure, there has been no satisfactory method of removing the growth at the first surgical intervention All surgeons have experienced the disappointment of finding that a carcinoma, previously judged operable, has meanwhile become too advanced for curative resection or even for palliation Often the interval between formation of the colostomy and the second operation is unduly protracted because of postoperative complications, such as wound sepsis or chest complications, or because of administrative errors, such as shortage of beds or operating time, or sometimes delay in acquiescence by the patient In this way valuable time is lost.

Admittedly occasional cases look inoperable at the earlier inspection, but become more easily resectable when secondary infection and œdema have subsided after colostomy It must be every surgeon's wish to get the carcinoma away as soon as it is discovered, but with the exception of the Paul-Mikulicz procedure and the somewhat unorthodox method of immediate resection and anastomosis, all other methods involve some delay

Technical Considerations

Resection of carcinoma of the colon in the presence of obstruction is not to be undertaken lightly, nor by the "occasional" surgeon, and it should be reserved only for selected cases Handling of the distended coils of bowel is easier where the ileocæcal valve has become incompetent, giving partial decompression of what was formerly a closed-loop obstruction in the colon

The operation is probably best reserved for cases where the growth is above the peritoneal shelf, for if the rectum is mobilised at the first operation difficulty is found in restoring continuity, as in case 4 The build of the patient is important, in case 3 extreme thinness made the operation exceptionally easy

Decompression of the bowel by means of a sucker, which is often very disappointing, is probably best performed *outside* the abdomen after the bowel has been brought to the exterior, as contamination is less likely The temporary colostomy is best sited at the upper end of the paramedian incision, as it facilitates dissection at the second operation Reconstitution can be deferred indefinitely, and need only be undertaken when the patient's general health is at its optimum.

Summary

A method is described of resecting carcinoma of the colon in the presence of obstruction Illustrative case-histories are given

A plea is made for this procedure in selected cases By this means the growth is removed at the earliest possible time, and the prognosis possibly thereby improved. Also the total duration of illness is shortened.

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PHYSICAL DISORDERS IN PSYCHIATRIC ILLNESS

A STUDY OF 209 CONSECUTIVE ADMISSIONS

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It is well known that a high proportion of patients presenting as general medical or surgical problems, and diagnosed with reasonable confidence as having some organic disease, are eventually found to have no significant physical abnormality In a recent study, using the Cornell medical index, Culpan et al (1960) found that of 95 new patients attending the medical outpatient department of a non-teaching hospital, 15% of men and 36% of women were emotionally disturbed, in gynæcological outpatients the figures were even higher—i e, 52% of 60 new attendances

Coming from a general medical to a psychiatric unit, I have been impressed by how often the converse is true, and in particular by the number of purely physical conditions initially diagnosed as "functional" Of course, the problem is not an "either or" one, but rather it depends to what extent physical disorders or findings are causal, concomitant, consecutive, or coincidental in psychiatric practice In 1949 Marshall studied the problem in this unit, and found that no fewer than 44% of 175 patients admitted had some physical state requiring attention I have made an investigation on similar lines

The Study

This psychiatric unit has forty-four beds (half male and half female) All patients were seen by one of the medical staff before admission to the unit except for a few transferred direct from other hospitals Between June, 1959, and February, 1960, inclusive, 209 patients (100 men and 109 women) were admitted The case-histories and nursing records of this group have been examined, and the principal diagnoses were

Endogenous depression (including involutional depression)	58
Schizophrenia	35
Reactive depression	22
Hysteria	15
Alcoholism	15
Anxiety state	12
Personality disorder and psychopathy	11
Drug addiction (barbiturates, codeine co , dexamphetamine, pethidine, morphine, carbromal, and trichloroethylene—1 each)	7
Hypomania	7
Toxic confusional states (barbiturates—2, disulfiram ('Antabuse') and bromide—1 each)	4
Arteriosclerotic and senile dementia	4
Hypochondriasis	3
Epileptic sequelæ	2
Neurasthenia, depersonalisation/derealisation, and old general paralysis of the insane (1 each)	3

There was also a group of 11 patients (5%) in whom major physical disease represented the principal diagnosis, but who were referred as having only "functional" illness, these are summarised in table I It should be

TABLE I—PHYSICAL ILLNESS PRESENTING AS "FUNCTIONAL" SYNDROMES

Case no	Diagnosis of referring doctor	Final diagnosis
Intracranial disease		
1	Postinfluenzal depression	Left frontal glioma
2	Loss of sense of time	Right frontal secondary
3	Anxiety from overwork	? Alzheimer's disease
4	Reactive depression to strokes	Left internal-carotid thrombosis
Extracranial disease		
5	Neurotic reaction to prison sentence	Uræmia ? cause
6	Involutional depression	Bronchial carcinoma with superior-vena-caval obstruction
7	Hysteria ? Simmond's cachexia	Tuberculous lung abscess
8	Hysterical reaction to bronchitis	Cor pulmonale and pneumonia
9	Reactive depression after stroke	" "
10	Post-head-injury defects	Toxic confusion from empyema
11	Senile dementia	Arteriosclerosis and uncontrolled diabetes

noted that in all cases, except nos 4, 5, 8, and 11, physical illness was diagnosed when the patient was first seen, though often the exact diagnosis was made only after admission to hospital The term " causal " is applicable to them all The following case-summaries, which are representative of this group, illustrate how patients' complaints may be misleading unless the situation is further elucidated

CASE 1 —A 54-year-old hotelier complained of listlessness, lack of interest, inertia, and poor concentration after an attack of " influenza ", which had been accompanied by much vomiting, 2 months previously He admitted to headache only on questioning He was apathetic and disorientated in time and place, with gross impairment of recent memory He had papillœdema of the left eye, but no other neurological signs Ventriculography revealed a large tumour of the left frontal region, and at craniotomy an extensive glioma was removed by frontal lobectomy Postoperative cerebral œdema developed, and the patient died

CASE 3 —An optician of 45 complained that his work had got on top of him, he felt depressed, was unable to concentrate, and found difficulty with his accounts He was superficially well preserved and appeared depressed, but he was slightly dysphasic and showed some lability of mood He was able to read only slowly and hesitantly, was virtually acalculic, and showed impairment of recent memory He also had complete finger agnosia, and left-right uncertainty, thus presenting the picture of Gerstmann's syndrome Ventriculography revealed cerebral atrophy, cortical biopsy was not done

TABLE II—" CONCOMITANT " PHYSICAL CONDITIONS APPARENTLY CONTRIBUTING TO THE ONSET OF PSYCHOLOGICAL ILLNESS

Physical conditions	No of patients
Central nervous system Head injury (3), epilepsy (2); cerebral thrombosis (3), hypertensive encephalopathy, subarachnoid hæmorrhage, general paralysis of the insane, postencephalitic neurasthenia, chemopallidectomy	13
Respiratory system Influenza (2), pneumonia, asthma	4
Cardiovascular system Hypertension (2), angina pectoris, cardiac failure, coronary thrombosis	5
Gynæcological conditions (excluding menopause) Puerperium (3), amenorrhœa, dysmenorrhœa, abortion	6
Orthopædic conditions Prolapsed intervertebral disc, fractured cervical spine, generalised osteoporosis, fractured ankle	4
Oropharynx Osteomyelitis of jaw, tempero-mandibular arthritis, chronic pharyngitis	3
Arteriosclerosis	3
Alimentary system Hæmatemesis from gastric ulcer, fissure-in-ano	2
Genitourinary system Renal and testicular tuberculosis	1
Endocrines Hypothyroidism	1
Skin Bromide-sensitivity rash	1
Total	43 (21%)

CASE 5 —A businessman of 47 complained of profuse vomiting, loss of weight, inability to taste, depression, and lack of energy Investigations by his own doctor had proved negative, and, as he had recently served a prison sentence for income-tax offences which had ruined his career, his illness had been considered psychogenic He was pale, with a dry scaly skin For 36 hours after admission he was anuric and he was found to have a blood-urea of 260 mg per 100 ml, with a secondary anæmia (hæmoglobin 7 4 g per 100 ml) His urine contained no protein, he was not hypertensive, and had no retinal changes With conservative treatment, diuresis started Renal biopsy was not possible because his blood-urea remained at 200 mg Hence the diagnosis remains uncertain, though chronic nephritis is most likely

CASE 6 —A 54-year-old housewife complained of irritability, insomnia, loss of weight, depression and a poor memory, and also of a dry cough and generalised skin irritation Her social situation was difficult, because her once affluent husband's financial position had declined Her condition had been investigated in hospital 5 months previously, and, as no physical cause could be found for her illness, she had been referred to a psychiatrist, who had made a diagnosis of involutional depression and given electroconvulsive therapy She looked depressed and ill, and she had clinical evidence of superior-vena-caval obstruction, with one hard supraclavicular lymph-node Her memory for recent events was poor, and she showed lability of mood Chest X-ray revealed a large mass in the anterior mediastinum, and biopsy of the supraclavicular node showed bronchogenic carcinoma Carotid arteriography showed no evidence of cerebral secondaries Radiotherapy reduced the size of the mass, and with relief of the caval obstruction her mental state improved

TABLE III—" CONSECUTIVE " PHYSICAL DISORDERS APPARENTLY RESULTING FROM PSYCHOLOGICAL ILLNESS OR ITS TREATMENT

Physical disorders	No of patients
Lesions resulting from suicidal attempts (2 before admission)	3
Liver damage from alcohol	3
Pulmonary embolism from deep-vein thrombosis of legs whilst having phenelzine therapy	1
Deep (1) and superficial (1) venous thrombosis of legs whilst having phenelzine therapy	2
Chlorpromazine jaundice	2
Chlorpromazine skin reactions urticaria (1), maculopapular rash (1)	2
Imipramine skin reaction (urticarial)	1
Liver damage (latent) from iproniazid	1
Total	15 (8%)

CASE 7 —A housewife of 26 had complained of headaches and various aches and pains associated with much weight loss, since having a baby 4 years previously Investigation by her own doctor and an ear, nose, and throat specialist had proved negative, and they thought she was reacting hysterically to a difficult marital situation She had had mass miniature radiography a year before admission to the unit Physical examination was negative, but chest radiography revealed a large lung abscess in the left lower lobe Her sputum teemed with acid-fast and alcohol-fast bacilli On triple antituberculous therapy she has greatly improved, but may need surgical treatment

CASE 10 —A slate miner of 44 had sustained a head injury whilst driving under the influence of drink in West Africa In hospital there, after regaining consciousness 24 hours later, he became progressively disorientated, aggressive, and deluded in a paranoid way He was flown back to this country with the diagnosis of post-head-injury syndrome On admission to the unit he was pyrexial and cachectic, and showed a toxic confusional picture He had a right pleural effusion, and aspiration revealed foul green pus laden with staphylococci With antibiotics and repeated chest aspiration his physical and mental condition returned to normal

TABLE IV—SIGNIFICANT PHYSICAL CONDITIONS APPARENTLY COINCIDENTAL TO PSYCHIATRIC ILLNESS

Physical condition	No of patients
Respiratory system	
? Active pulmonary tuberculosis (2), chronic bronchitis (3), upper-respiratory-tract infections (4)	9
Alimentary system	
Dental conditions (8), peptic-ulcer symptoms (2), hæmorrhoids (2)	12
Cardiovascular system	
Symptomless mitral incompetence (1), auricular fibrillation (1), hypertension (2)	4
Orthopædic conditions	
Fractured ankle, prolapsed intervertebral disc, fractured jaw	3
Gout	1
Idiopathic hypercholesterolæmia	1
Severe varicose veins and varicose eczema	1
Ophthalmic conditions (excluding errors of refraction)	1
Iron-deficiency anæmia	2
Total	*34 (16%)*

Of the remaining patients, 69 (34%) were found to have, or developed whilst in hospital, physical illnesses which required attention or further investigation 18 (9%) of these had multiple physical abnormalities The physical conditions are detailed in tables II–IV, and the terms concomitant, consecutive, and coincidental may be respectively employed

Table III shows that 9 patients (4%) developed presumably iatrogenic conditions whilst having modern drug therapy 3 of these had venous thrombosis of the legs whilst receiving phenelzine, and 1 also had a small pulmonary embolism None of them was particularly debilitated, or confined to bed, before the thrombosis occurred, hough 2 had minor varicose veins I have not seen nother report of this complication of phenelzine therapy

Discussion

Many patients in whom their own doctors have found no physical abnormality are being referred to the psychiatric outpatient clinics instead of to medical outpatient clinics Greater vigilance is therefore required on the part of psychiatrists to avoid labelling physical, nd potentially treatable, disease as "functional"

Comroe (1936) was one of the first to become aware of his situation, he found that of 100 patients in a general medical clinic with the diagnosis of neurosis, 24% developed organic disease within 8 months, and in many of these it was present when the original diagnosis was made Meyer (1958), in a general review of the relation of psychiatry to surgery, has emphasised that because symptoms arise in the midst of an emotional crisis the possibility of organic disease is not excluded. This is further borne out by cases 5, 6, and 7 of the present study, in which a spurious psychogenesis had been attributed to real physical illness The likelihood of such a mistake will be considerably lessened if one remembers that neurotic reactions are rare in patients of mature years with good previous personalities and no past history of similar episodes

Cases 1–3, 6, 10, and 11 all showed organic mental syndromes, of these, cases 1, 3, and 6 in particular complained a priori of none of the usual symptoms, but of more nebulous things like depression and listlessness Organic symptoms should be specifically looked for and inquired after, and the scheme for examination put forward by Mayer-Gross (1954), with particular care in testing for orientation, memory, attention and adaptability, lability of mood, and use of numbers, can be applied simply and quickly in all cases

A psychiatric opinion is often requested after patients have been "through the mill" in other special departments, and therefore the physical states which may be found are uncommon or atypical. For example, Eilenberg and Scobie (1960) have emphasised the tendency to misinterpret the symptoms of acute porphyria as hysterical

Finally, the need for a full physical examination of every psychiatric case, irrespective of whether the patient has been referred from another doctor or hospital, is self-evident but often forgotten, as is well illustrated by cases 6 and 10 Furthermore, the full use of all ancillary diagnostic aids is essential Every patient admitted to this unit has a routine urine examination, chest X-ray, blood-count, erythrocyte-sedimentation rate, and Wassermann reaction Many important physical conditions would have been missed without.

Summary

The physical disorders amongst 209 psychiatric inpatients have been analysed

In 5% major physical illness, first discovered on admission to a psychiatric unit, was the principal diagnosis In 21% physical conditions contributed to the onset of psychiatric illness, in 8% they resulted from it, and in 16% they were unrelated to it.

The dangers of imputing a spurious psychogenesis, and of overlooking organic mental syndromes, must be avoided.

A full physical examination, with radiological and pathological investigation if indicated, is important.

I am grateful to Dr Desmond Curran, Sir Paul Mallinson, and Dr Maurice Partridge for permission to study and report on their cases, and to Dr Curran in particular for much helpful advice and encouragement.

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CYTOMEGALIC INCLUSION DISEASE AND PNEUMOCYSTIS CARINII INFECTION IN AN ADULT

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CYTOMEGALIC inclusion disease is a viral infection which has been recognised in infants for some years (Farber and Wolbach 1932, Wyatt et al 1950, Seifert 1954, Nelson and Wyatt 1959) It may be localised to the salivary glands, when it is usually found incidentally at necropsy, or it may be a severe, sometimes fatal, generalised illness (Worth and Howard 1950) In adults, cytomegalic inclusion disease is rare and takes a different form It may be confined to a single organ in association with other diseases, notably those of the reticuloendothelial system (Hamperl 1956) In a more generalised form, it is often accompanied by other systemic diseases (Fisher and Davis 1958)

Pneumocystis carinii is thought to be a protozoon and was first alleged to be responsible for interstitial plasma-cell pneumonia of infants by Vaněk and Jirovec (1952)

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This disease was initially recognised in central Europe (Rossle 1923, 1928, Ammich 1938) Later, cases were reported from Scandinavia (Linell 1949, Gormsen 1950), Great Britain (Baar 1955), North America (Lunseth et al 1955), and Australia (Reye and ten Seldam 1956) An association between this condition and cytomegalic inclusion disease has been observed in infants (Dittrich and Seifert 1953, Baar 1955, Berdnikoff 1959) This form of combined infection appears to be extremely rare in adults (Hamperl 1956, Symmers 1960)

Clinical Report

A man, aged 25, was admitted in April, 1959 For two years he had had chronic gingivitis which improved temporarily after gingivectomy in November, 1958 Throughout 1958, he had had variable non-irritant lesions on the skin of his back and shoulders He attended elsewhere for dermatological advice during this time, the diagnoses included neurodermatitis, eczema, and tinea, and he was treated with X rays, local hydrocortisone (1% cream), and chlortetracycline (1% cream)

His general health was good until December, 1958, he then gradually developed breathlessness on exertion, nocturnal sweats, anorexia, loss of weight, tiredness, and fever He had a cough, producing mucopurulent sputum with a few scanty hæmoptyses He had had slight pruritus ani for some years, and had hæmorrhoids which bled occasionally In February, 1959, a painful, indolent anal fissure developed, and gradually extended backwards and forwards from the anal margin This enlarging ulcer had a shallow edge and a deep centre. In April, 1959, a small papule appeared in one nostril The papule ulcerated and slowly increased in size

He was wasted, febrile, and ill There was moderate generalised gingivitis A few scaly brownish lesions were seen on the skin of his back and shoulders There was no enlargement of lymph-nodes, and no abnormalities were found in the cardiovascular system (blood-pressure 120/75 mm Hg), lungs, abdomen, or central nervous system. The anal ulcer extended 3 in in the natal cleft behind the anus and 1 in anteriorly, it was covered by a purulent exudate. A small papule was seen at the tip of the left nostril

Investigations

The hæmoglobin ranged from 94 to 108% (13 9–16 0 g per 100 ml) and the white-cell count from 7300 to 10,800 per c mm (the differential count was normal) His erythrocyte-sedimentation rate was also normal (2 to 8 mm in the first hour) except during an attack of bacterial pneumonia when it rose to 30 mm The serum-albumin was between 3 3 and 4 5 g per 100 ml, falling to 2 1 g on Aug 20, 1959 The serum-globulin was between 2 3 and 2 4 g per 100 ml

Serial chest radiographs showed fine nodular opacities throughout both lungs, with partial clearing after the administration of steroid drugs The sputum was examined many times, acid-fast bacilli were not seen and all cultures for *Mycobacterium tuberculosis* were negative The Mantoux test was negative at a strength of 1/10 The fæces contained no pathogenic organisms, and swabs from the anal fissure showed debris and gram-negative bacilli, culture produced a growth of *Bacillus proteus* and a coliform organism Blood-cultures were repeatedly sterile The Wassermann reaction and the Kveim test were both negative Examination of the sternal marrow showed a nucleated-cell count of 178,000 per c.mm. There was generalised hyperplasia of all normal elements and plasma cells were present Tissue was taken for microscopic examination from the anal and nasal lesions, and a scalene node was also removed The anal lesion consisted of a non-specific granulomatous ulcer, the nasal lesion was ulcerated, granulomatous, and densely infiltrated with polymorphonuclear leucocytes and lymphocytes, there were no eosinophils or vascular damage The scalene node showed some reactive hyperplasia but was otherwise normal

Progress and Treatment

An initial diagnosis of miliary tuberculosis was made in view of his high fever, severe constitutional symptoms, and the radiological findings He was treated with streptomycin 1 g daily, isoniazid 100 mg twice daily, and *p*-aminosalicylate 6 g twice daily for twelve weeks There was no response to treatment and, because of the negative reaction to tuberculin, the diagnosis was abandoned Other diagnoses which were considered included sarcoidosis, the reticuloses, and Wegener's granulomatosis After two months, prednisone 10 mg three times daily was added to the antituberculous regimen This produced a temporary improvement in his symptoms, the pyrexia subsided for several weeks, his appetite improved, and he gained weight The anal lesion, however, had progressed remorselessly to involve a wide area of his buttocks, extending several inches on each side of the natal cleft (fig 1a) The nasal lesion broke down into a chronic ulcer which eroded the nasal cartilages and spread to the lip (fig 1b) An indolent paronychia of the left index finger developed In the last month of life, fresh ulcers appeared on the dorsum of the tongue and the lower lip Local radiotherapy was given to the ulcerated areas, but without any convincing benefit Three weeks before

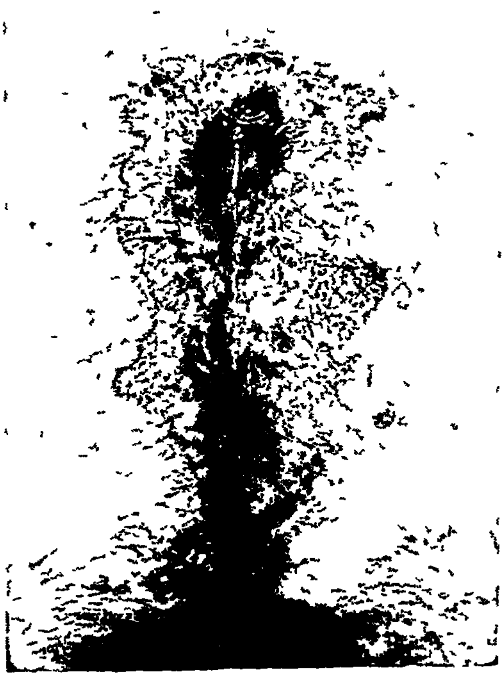

Fig 1a—Perianal ulceration.

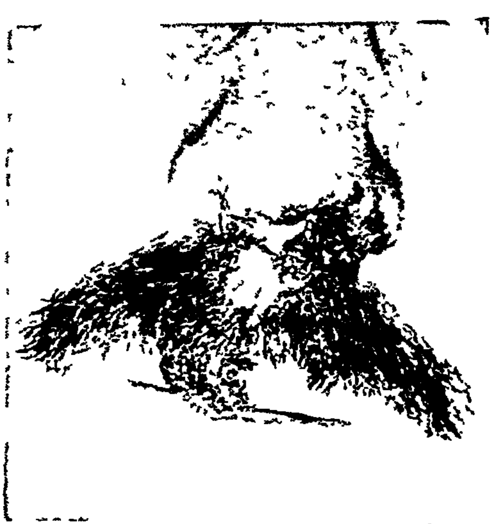

Fig 1b—Ulcer of nose spreading to upper lip

death he had severe bronchopneumonia which partially responded to treatment with erythromycin 500 mg six-hourly, and chloramphenicol 500 mg six-hourly for ten days, but he steadily became weaker, dying some four and a half months after admission Latterly there was central cyanosis with increasing tachypnœa and early clubbing of the fingers

Postmortem Appearances

External

The body was severely emaciated The epidermis lying between the nasolabial folds was largely desquamated from an underlying smooth, moist dermal surface The perianal ulcer, its base covered by serofibrinous exudate, extended over the buttocks with an ill-defined, undermined edge The nasal and finger lesions were similar, though smaller Numerous small lesions, some pustular, others dry and encrusted, were distributed irregularly over the skin of the thorax, abdominal wall, scapular regions, and inner aspects of thighs

Internal

The lining membranes of the nose, mouth, pharynx, and larynx were ulcerated and covered with purulent exudate, ulcerated plaques were present on the dorsum and lateral margins of the tongue. The trachea was congested and contained a little mucopus, but was not ulcerated.

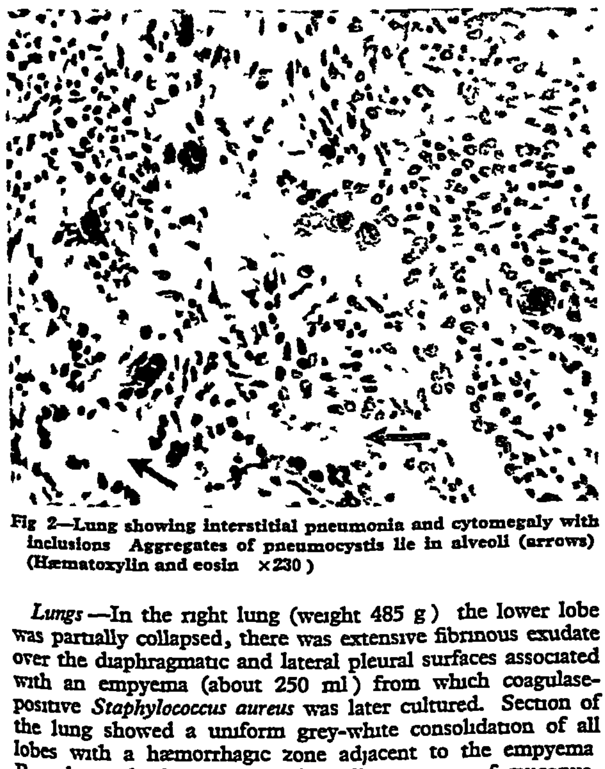

Fig 2—Lung showing interstitial pneumonia and cytomegaly with inclusions Aggregates of pneumocystis lie in alveoli (arrows) (Hæmatoxylin and eosin ×230)

Lungs —In the right lung (weight 485 g) the lower lobe was partially collapsed, there was extensive fibrinous exudate over the diaphragmatic and lateral pleural surfaces associated with an empyema (about 250 ml) from which coagulase-positive *Staphylococcus aureus* was later cultured. Section of the lung showed a uniform grey-white consolidation of all lobes with a hæmorrhagic zone adjacent to the empyema Bronchi at the base contained small quantities of mucopus, the remaining bronchi contained mucoid material only The pulmonary arterial tree was normal

The left lung (weight 480 g) was of firm consistence, its cut surface showed extensive areas of grey-white consolidation sharply defined from limited areas of aerated tissue. Small quantities of mucoid material were present, mainly in the bronchi of the lower lobe The main pulmonary arteries appeared normal The hilar and mediastinal lymph-nodes were moderately enlarged and rather fleshy, with foci of carbon pigmentation

Other organs —The pericardial sac contained approximately 7 ml of brown-stained fluid and showed a slight fibrinous exudate over the apex.

The spleen (210 g) was moderately enlarged and soft The liver (1950 g) was enlarged and rather flabby, with a pale cut surface, showing occasional hæmorrhagic foci The lobular pattern was maintained

Fig 3—Lung Cytomegalic inclusion cell showing typical intranuclear and intracytoplasmic inclusions (Giemsa ×700)

The only lesion seen in serial sections of the brain was a solitary, pale brown, circumscribed focus 0 5 cm in diameter situated in the cortical grey matter of the left parietal lobe.

Histological Examinations

The lungs showed a fairly generalised, bilateral interstitial pneumonia The alveolar septa were thickened and infiltrated, mainly by small lymphocytes and, to a lesser extent, by plasma-cells The alveolar lining epithelium was cubical in many areas and frequently shed into the alveolar lumina which contained numerous lipid-laden phagocytes Large cells, typical of cytomegalic inclusion disease, were present in all lung fields, being particularly striking in some areas (fig 2) The intranuclear inclusions were strongly basophilic, they stained red or red-brown in phloxine-tartrazine preparations and blue with Mallory's phosphotungstic-acid/hæmatoxylin. Between the intranuclear inclusion masses and the nuclear membrane, which often showed margination of nuclear chromatin, there was in most instances a clear halo Within the cytoplasm there were clusters of small inclusions, shown well in Giemsa preparations as small blue bodies (fig 3) Scattered irregularly throughout the lungs, sometimes densely, were honeycomb masses of light-refracting bodies, characteristic of the cysts of *Pneumocystis carinii* These masses reacted strongly to periodic-acid/Schiff and to the methenamine silver stain of Gomori, and with a lesser intensity, to the Weigert-Gram (fig 4) and Gridley stains (1953) Some of the cysts contained four or eight distinct spores, others

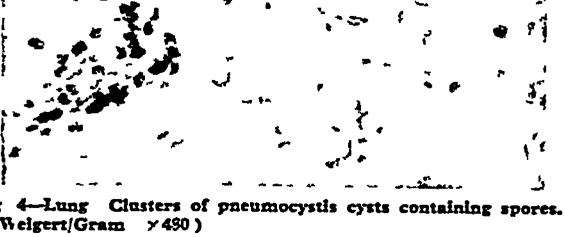

Fig 4—Lung Clusters of pneumocystis cysts containing spores. (Weigert/Gram ×480)

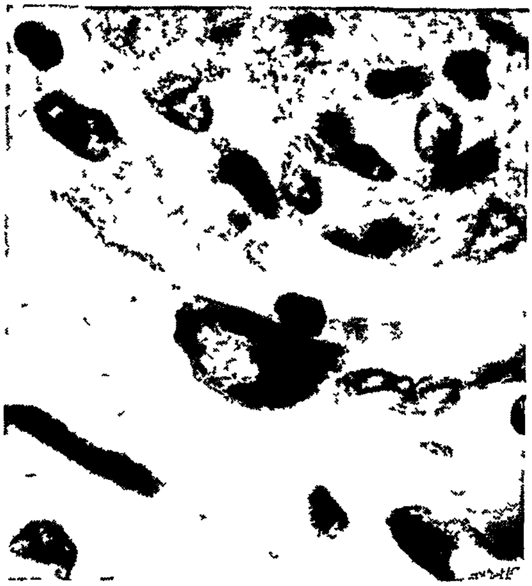

Fig 5—Skin lesions Capillary in granulation tissue showing inclusions in nuclei and cytoplasm of endothelial cell (H & E ×870)

appeared degenerate and void of spores Occasional spores or spore-bearing cysts were located with the alveolar septa

The Skin Lesions

The lesions around the mouth and in the perianal region were non-specific granulomatous ulcers Secondary infection contributed to most of the lesions in the mouth or pharynx A careful search failed to show evidence of parasitic and fungal infection in these sites In the circumoral and perianal lesions, and in the ulcerated plaques on the tongue, intranuclear inclusions were found in some of the cells (presumably endothelial) lining, or in close relation to, the lumina of the capillaries of the granulation tissue (fig 5)

Elsewhere, the smaller skin lesions consisted of encrusted, non-specific superficial ulcers, or small intradermal abscesses Occasional small, herpetiform vesicles occurred in the hypertrophic squamous epithelium of the tongue

The cellular focus of the brain lesion consisted of astrocytic cells with granular nuclei, oligodendrocytes, microglial cells, and a few surviving neurones in a rather vascular stroma Search for both inclusion bodies and protozoa proved negative, although unusual amounts of extracellular granular material positive to periodic-acid/Schiff were present The nature of this lesion is uncertain, the histological appearances suggest either an early astrocytoma, though in an unusual site, or alternatively a hamartomatous glial nodule

Discussion

The initial clinical diagnoses were tuberculosis or a reticulosis The outstanding features at this time were the severe constitutional symptoms and fever, out of keeping with the relatively slight clinical findings, the major lesion was the already advanced anal ulcer Tuberculosis was excluded by the negative Mantoux test, failure to isolate any organisms, and failure to respond to appropriate treatment A reticulosis seemed unlikely in view of the biopsy reports Sarcoidosis was considered but later progress and the results of the investigations did not support this diagnosis

The progressive extension of the nasal ulcer finally suggested the diagnosis of Wegener's granulomatosis, the general features, together with the ulceration, appeared typical of this condition (Walton 1958), though there was no involvement of the kidneys Anal ulceration, as seen in our patient, does not appear to have been described, though the case of Short (1957) had shallow necrotic ulcers over the buttocks Wegener's granulomatosis was the presumptive clinical diagnosis at the time of death

From the pathological point of view, the main interest lay in the lung and skin lesions Histologically there was no evidence of Wegener's granulomatosis The main pulmonary lesion was a severe interstitial pneumonia associated with cytomegalic inclusion disease and a patchy pneumocystis infection The patchiness of this infection and the pulmonary macrophage response indicated some degree of resistance on the part of the host, whose death was finally hastened by a terminal staphylococcal pneumonia and empyema This is in contrast to the overwhelming pulmonary protozoal infections encountered in the majority of infants suffering from pneumocystosis

The possibility of Behçet's disease was rejected because of the distribution and progressive nature of the skin lesions, together with absence of eye and joint symptoms, and central nervous system lesions (France et al 1951, Curth 1952) The only specific features of the lesions in the skin were the presence of intranuclear and intracytoplasmic inclusions in the endothelial cells of related capillaries These are an accepted feature of cytomegalic inclusion disease in its generalised form (Symmers 1960) Hartz and van de Stadt (1943) described similar inclusions in the capillaries in a biopsy specimen from a pedunculated anal tumour in a 35-year old coloured woman

Generalised cytomegalic inclusion disease in the adult has been described in association with toxoplasmosis and myeloid metaplasia (Hemsath and Pinkerton 1956), myeloid leukæmia (Fisher and Davis 1958), and with *Pneumocystis carinii* infection and severe systemic diseases (Symmers 1960) In our case, if one accepts the staphylococcal lung infection as a terminal event, no severe underlying disease was found, the small brain lesion being regarded as fortuitous Although agammaglobulinæmia or hypogammaglobulinæmia could not be excluded on the data available, the normal total serum-protein levels and abundance of plasma-cells in the bone-marrow and tissues make this unlikely Steroid therapy, however, probably contributed to a decreased host resistance in this case, thus encouraging extension of the infections, and possibly allowing these saprophytic organisms to adopt a pathogenic role This possibility has been demonstrated with a wide variety of bacteria, viruses, protozoa, and fungi (Kass and Finland 1953)

The pattern of generalised cytomegalic inclusion disease may vary, but the lungs, adrenals, liver, spleen, and kidneys are most commonly involved Lesions varying from early degenerative changes to frank cellular necrosis have been described in these organs The view advanced by von Glahn and Pappenheimer (1925) that this is a viral disease has been confirmed by the recent experimental work of Smith (1956) which also supported the probable species-specificity of the virus Nor is the virus purely epitheliotrophic—for example, Vogel (1958) found specific inclusions in fibroblasts, heart-muscle cells, and mesothelial and endothelial cells, in a 10-year-old boy dying from the disease He also successfully reproduced comparable endothelial inclusions in the capillaries of experimental granulomata in mice inoculated with mouse inclusion virus

The association with *Pneumocystis carinii* infection was of further interest This form of alleged protozoal infection has now become an established pædiatric hazard with a predilection for premature, debilitated, or congenitally afflicted infants (Vaněk and Jírovec 1952, Hamperl 1952, Herzberg et al. 1952), but it has very rarely been found in adults Isolated adult cases have been reported, associated with other concurrent diseases (Meer and Brug 1942 Jírovec and Vaněk 1955), whilst Hamperl (1956) demonstrated the infection in a case of fatal inclusion pneumonitis reported by McMillan (1947) and suggested the probability in two similar cases of Wyatt et al (1953) Simultaneous pneumocystis and cytomegalic inclusion infections have also been described by Berdnikoff (1959) in an infant. The association of these two apparently separate and normally saprophytic infections is interesting, and perhaps not entirely fortuitous, especially since the nature of the pneumocystis organism has not yet been determined In due course a closer relationship may be established. It is important to recognise their potential pathogenicity and their ability to produce, either alone or in combination, fatal infections in man.

There is some evidence that this danger is increased by prolonged treatment with steroids and antibiotics (Symmers 1960) Possibly more cases will occur because of the increasing use of these drugs At present, there is no effective treatment.

Summary

A fatal case of combined cytomegalic inclusion disease and *Pneumocystis carinii* infection is described in a man aged 25 The main clinical features were a long-continued and progressive oronasal and perianal ulceration with severe constitutional disturbance, followed by increasing pulmonary distress ending in bronchopneumonia and empyema

At necropsy, the main lesions were restricted to the lungs and skin, they included extensive grey-white consolidation of both lungs associated with staphylococcal empyema, severe ulceration in and around the mouth and in the perianal region, together with more generalised ulceration of the skin. Histologically the pulmonary lesion proved to be a severe interstitial pneumonia associated with cytomegalic inclusion disease and *Pneumocystis carinii* infection The skin lesions were explicable in terms of giant-cell inclusion disease.

Very rarely both infections described have been found together in adults in association with serious underlying diseases, no underlying disease was identified in this patient. The nature of the infections is discussed and reference is made to the risk of converting these saprophytes into pathogenic organisms by prolonged treatment with steroid drugs and antibiotics

We are grateful to Dr C S D Don for permission to publish this case, to Prof A C P Campbell and Prof H Hamperl (Bonn) for help in preparation, and to Mr N Mowat and Mr G Saville for technical assistance

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PSEUDOTUMOUR OF THE ORBIT AND WEGENER'S GRANULOMA

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The clinical condition known as "pseudotumour of the orbit" is a well-recognised, though relatively rare, lesion. Its cause is unknown, but recent work suggests that it belongs to the group of diseases which show chronic inflammatory reaction to a non-bacterial agent. This group includes polyarteritis and Wegener's granuloma (Walton 1956a and b, 1958) Duke-Elder (1952) describes orbital pseudotumours as "cases which are difficult to differentiate clinically from an orbital tumour, but which, on pathological investigation or by their resolution under treatment, are shown to be granulomata of chronic inflammatory origin"

Our case was diagnosed clinically and histologically as pseudotumour of the orbit. At necropsy the condition was found to be Wegener's granuloma, an ulcerative, granulomatous lesion primarily involving the respiratory tract, and, in this case, with secondary involvement of the orbital tissue from the nasal sinuses

Several fatal cases of Wegener's granuloma of the mouth and nose have been seen in Cumberland during the past thirty years, three of which were published by Walton (1956b), who subdivides the condition into three types (1) associated with polyarteritis, (2) typical malignant granuloma usually involving the upper respiratory tract, and, though not histologically malignant, invariably fatal, and (3) granuloma gangrænescens—a histologically malignant sarcomatous lesion associated with extensive local destruction

In our patient a granulomatous lesion, initially involving the orbit and ethmoidal sinus, eventually spread to the skull bones and cranial cavity Later the lungs became involved, with cavitation and a purulent sputum The disease progressed steadily, and proved fatal in two years At postmortem examination, polyarteritis was found, with ischæmic necrosis and scarring of the kidneys

Case-record

A woman, aged 35, was first seen in June, 1956, when she complained of diplopia and orbital pain of four weeks' duration. The left eye was found to be proptosed and a firm swelling, painless on pressure, was palpable under the lower lid, attached to the medial margin of the orbit, pushing the eye upwards and outwards Both eyes were healthy, and vision was 6,6

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in each, the left lacrimal duct was freely patent, and an X-ray showed an opaque left maxillary sinus but no erosion of the bone The aural surgeon's opinion was that the nasal cavity was not the cause of the infection, though crowding of the left olfactory cleft was observed, with crusts which bled easily He considered that the sinus was being involved secondarily to the orbit. The sinus was punctured and washings contained purulent material, mainly necrotic tissue infiltrated by polymorphonuclear leucocytes and round cells No malignant cells could be seen, and no organisms grew on culture Conjunctival swabs were sterile, Wassermann and Kahn reactions negative, X-rays of chest and skull normal, and the Mantoux test negative at a dilution of 1/1000

At operation on Aug 16, 1956, a large solid non-encapsulated mass was found occupying the lower part of the orbit and infiltrating the inferior rectus and orbicularis muscles A good part of it was removed, but a flat extension went back to the apex of the orbital cavity and was inaccessible The histological report on this material stated that it was mostly fibrous tissue with numerous centres of inflammation, infiltrated with plasma-cells and polymorphs and with one or two "atypical giant cells" There was no evidence of sarcoidosis, tuberculosis, or tumour, nor could any organisms be demonstrated in the sections A section was sent to the Institute of Ophthalmology in London, where it was reported to be a "non-specific granuloma of orbit, commonly known as a pseudotumour of the orbit, the ætiology of which is obscure"

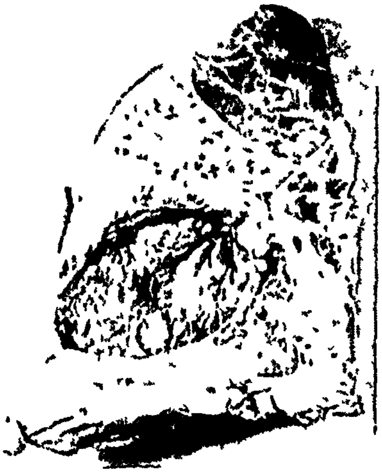
Fig 1—Lung with large abscess cavity in lower lobe

After a temporary improvement, the proptosis recurred and on Dec 4, 1956, the patient was referred to the neurosurgical unit in Newcastle, with increasing ptosis, ophthalmoplegia, papillœdema, and detachment of the retina On Dec 19 an orbital decompression was carried out, the roof and lateral wall of the orbit being removed, part of the tumour was excised It was reported to be histologically "chronic granulation tissue" Her sight improved after this operation, but ten months later the mass had enlarged, and, by pressure on the eye, caused acute glaucoma The eye was removed and the orbit exenterated A section was sent to the Institute of Ophthalmology and again it was reported to be a "pseudotumour of the orbit" The patient now developed bilateral inner-ear deafness which became extreme An increase in the size of the thyroid gland was observed, and this was confirmed by the increased absorption of radioactive ^{131}I, but there was no other evidence of hyperthyroidism The pain in the left orbit and left side of the face was increasing and was not controlled by simple analgesics In December, 1957, she was treated with deep X-ray therapy, antibiotics, and prednisone, without much response After this she developed severe anæmia and became totally deaf In January, 1958, a further intensive course of high-voltage X rays, combined with erythromycin, was given, because the condition was considered to be a malignant granuloma of the upper respiratory tract Considerable regression of the tumour mass resulted, with alleviation of the pain

By April, 1958, the patient had enlarged submaxillary lymph-nodes, severe anæmia, and sloughing of the left upper lid The orbital cavity was filled with granulations Proptosis of the right eye and enlargement of the right pre-auricular lymph-node developed A hard mass was palpable below the angle of the right mandible There was abundant purulent sputum and further therapy was considered useless She died at home on May 23, 1958

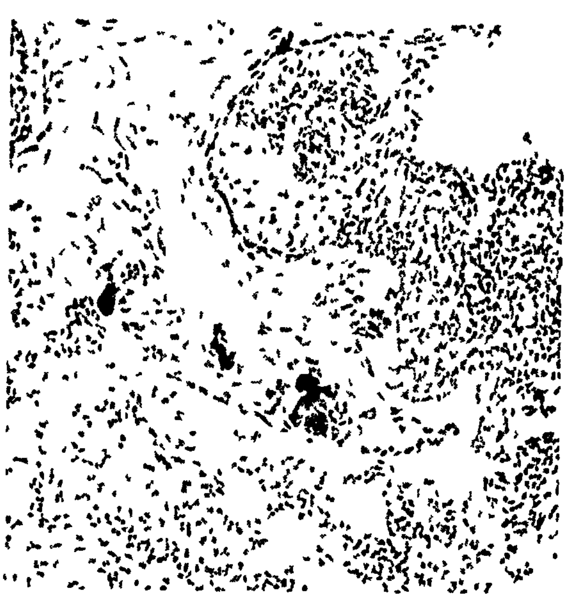
Fig 2—Squamous epithelial lining of lung abscess, with "eosinophilic" protein deposit among cells (×100)

Postmortem Findings

A large ulcerated area occupied the left orbit, which was completely destroyed and replaced by a putrefying abscess cavity This communicated with the ethmoid sinuses and extended into the cranial cavity over the inferior surface of the left frontal lobe There was no evidence of meningitis, or of infection or abnormality in the brain

Respiratory tract—There was no abnormality in the mouth or pharynx, but unfortunately the nose and sinuses were not examined in detail as the clinical notes were not available at the time of the postmortem examination The trachea and bronchi were filled with purulent sputum The right lung had a large, irregular, abscess cavity, 9×6 cm, in the lower lobe, lined by shaggy purulent granulations and containing foul-smelling pus (fig 1) The remainder of the lungs showed a diffuse bronchopneumonia and purulent bronchitis, but there were no other cavities and there was no evidence of tuberculosis Microscopically, the abscess cavity was *mostly lined by pyogenic granulations containing deeply stained giant cells Areas of* the abscess cavity were lined by squamous epithelium, and between certain of the cells were collections of pink-stained protein deposit similar to that seen in the capillary loops in periarteritis (fig 2) No histological evidence of tuberculosis or tumour was found

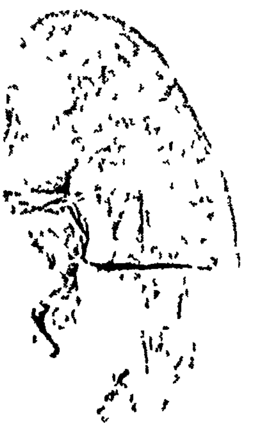
Fig 3—Kidney with depressed white scars caused by fibrosed areas

Cardiovascular system—There was no cardiac enlargement, arteriosclerosis, or evidence of hypertension

Urinary system—Both kidneys were irregular in shape, and through the capsule could be seen many pale areas suggestive of secondary tumour (fig 3) The capsule stripped easily, revealing multiple depressed scars approximately 1 cm in diameter On section, the pale areas were found to be wedge-shaped, with the apex pointing to the medulla From the naked-eye appearance, they were considered to be the result of ischæmic necrosis from endarteritis Microscopically these areas resembled the original tissue taken from the orbit The renal tissue was necrotic and could be recognised as an indifferently stained material in which shadows of glomeruli, tubules, and vessels were visible At the edge of the "infarcted" area, proliferating fibroblasts, along with lymphocytes and atypical giant cells, were present, and the glomeruli had a thickened capsule with the capillary loop obstructed by eosinophilic material A number of the glomeruli were fibrosed and surrounded by fibrous tissue (fig 4) The initial lesion appeared to be a glomerulitis with primary involvement of the capillary loop, but an explanation for the wedge-shaped necrotic zones could not be found, as there was no thickening or obstruction of the larger arteries or arterioles (fig 5)

Discussion

Both diseases—Wegener's granulomata and pseudotumour of the orbit—have been described in recent well-documented reports, but, so far as we know, recognition of the two conditions in the one patient has not been recorded Orbital involvement occurred in several of the cases quoted by Walton (1959a) which were not considered clinically as cases of pseudotumour, and Jackson (1958) likewise noted the frequency of involvement of the nasal side of the orbit, suggesting an association with the nasal sinuses and cavity Jackson also observed an association of eye lesions with a granulomatous lesion in the lung and considered pseudotumour to be a specific disease primarily related to the air-passages, but did not link it up with Wegener's granulomatosis

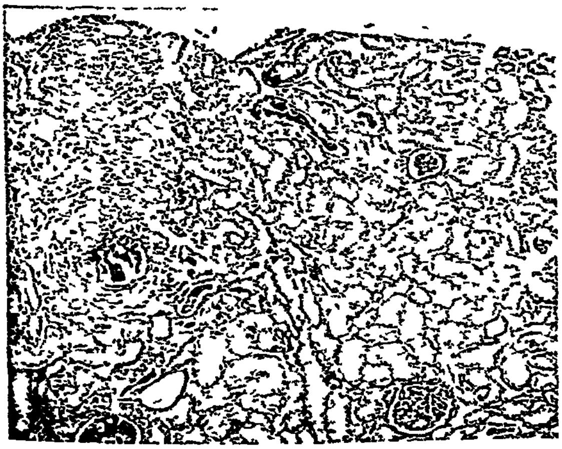

Fig 4—Kidney fibrosed area (×100)

In our case, the presenting symptom was the lesion in the left eye, and at an early stage an abnormality was observed in the corresponding side of the nose, which was considered to be secondary to the orbital lesion In spite of the obvious pulmonary lesion, the failure to respond to treatment, and the involvement of the ears (a feature recorded in many cases of Wegener's syndrome), the correct diagnosis was not suggested until just before death

The postmortem renal findings of glomerulitis, arteritis, and the multiple scars caused by the wedge-shaped granulomatous fibrosis, along with the pulmonary changes, is characteristic of a Wegener's granuloma An arteritis was observed in the spleen and pulmonary vessels as well as in the kidneys, and a peculiar eosinophilic protein material was found between the squamous epithelial cells lining the large abscess cavity in the lung This material resembled that found in systemic lupus erythematosus The similarity of the renal changes found in both Wegener's granuloma and lupus erythematosus has been noted by many In Walton's case of pseudotumour with polyarteritis (1959b), renal infarcts were shown but no granulomatous changes were seen, and only a few of the glomeruli showed fibrinoid changes in the capillaries

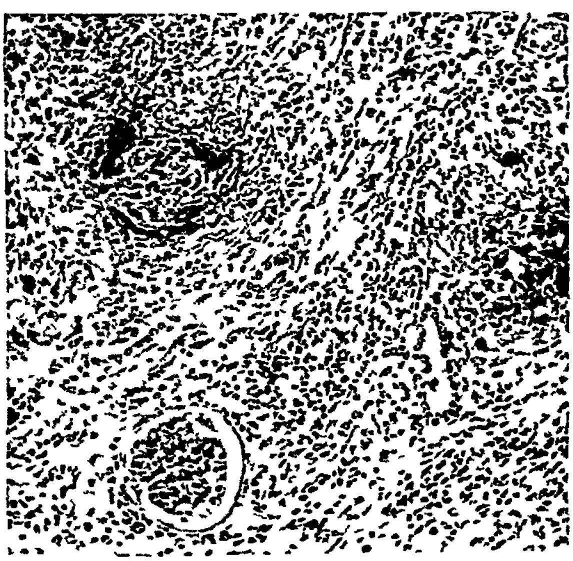

Fig 5—Kidney fibrosed glomerulus (×100)

The cause of both conditions is unknown No infective agent has been isolated, and, though Symmers (1960) demonstrated *Pneumocystis carinii* and cytomegalic inclusion bodies in his case, he concluded that they were the result and not the cause of the trouble A widely held view is that Wegener's granuloma and pseudotumour are iatrogenic diseases produced by the administration of antibiotics and sulphonamides This can be discounted because both conditions were recognised before either therapeutic agent had been invented A sensitivity to drugs has been observed in our case, as in most others For that reason, antibiotics, particularly streptomycin and the sulphonamides, are often blamed for aggravating both lesions and are never found to help

From relevant publications and the appearances in this case we consider that pseudotumour is an orbital manifestation of Wegener's granuloma and that both conditions are specific tissue reactions to an agent not so far identified

Summary

A case is presented of pseudotumour of the orbit and coexistent Wegener's granuloma, and it is suggested that the two conditions are linked ætiologically

We are indebted to Dr A C Ogilvie, who carried out the postmortem examination at Workington Infirmary, for a copy of his notes and for giving us the *specimens to study*, to Mr G F Rowbotham, of the neurosurgical unit, Royal Victoria Infirmary, Newcastle, for the use of his notes, and to Prof J B Duguid, Newcastle, who helped to solve the problem

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Preliminary Communications

INFRA-RED RADIATION THERMOMETRY IN CLINICAL PRACTICE

WHILE we were trying to devise a method of locating incompetent perforating veins in patients with varicose veins, it occurred to one of us (K Ll W) that the skin temperature might be greater at the point where a perforating vein " surfaced ", and that infra-red emission from the skin would, therefore, be increased This idea, though not so far very successful in application, proved a starting-point for a more general consideration of infra-red emission from the skin under normal conditions and in pathological states

It has long been known that skin (whether white or pigmented) behaves as a black-body radiator [1–4] and that infra-red emission from it therefore bears a direct relationship to the surface temperature [5] The measurement of skin temperature from infra-red radiation has great advantages over direct thermometry (e g , by thermocouples) because (1) the rays can be measured at a distance and contact with the skin is unnecessary, (2) it is very rapid, and (3) measurement at a distance yields an average reading for a small area of skin rather than for a point, and this tends to compensate for local variations in capillary tone

Infra-red waves emitted from the skin have a wavelength varying from 4 to 20μ, with a peak emission at 9μ, and highly sensitive instruments are available for measuring them It was decided that a Schwarz thermopile, fitted with calcium-fluoride window, transmitting wavelengths up to 11μ, was the most suitable detector available Measurements were made at a distance of 1 cm from the skin, the current produced by the thermopile being measured by deflection of a mirror galvanometer A contact thermocouple was used to verify the direct relationship between the infra-red emission and the surface temperature The deflection per degree centigrade was determined by comparison with the radiation from the blackened face of a Leslie cube at known temperature

CLINICAL APPLICATION

When clinical observations of infra-red radiation from the skin were to be made, the patient was unclothed and left in a room of constant known temperature for ten minutes Readings were then taken with the thermopile at 1 cm distant from the skin over the area of pathological signs, immediately followed by readings made on the same area of the other (normal) side of the body Our early observations were made over swellings which were obviously hot to touch and we were astonished to find that the skin temperature over a superficial abscess might be raised by as much as 5°C above the normal area on the other side On several occasions, temperatures 1°C or more above the rectal temperature were recorded An abscess in the rectus sheath was dermarcated by scanning it with the thermopile, and it was also found that regional lymph-nodes, enlarged by inflammation, were hotter than those on the contralateral part of the body

A series of breast swellings was next investigated The findings in this series are being reported more fully elsewhere 32 out of 34 carcinomata were hot as compared with the same area in the other breast—an observation already made by Lawson [6, 7] The temperature difference was often of the order of 2–3°C, and was measurable by relatively crude instruments

The rise in temperature over malignant tumours was not confined to breast cancers, but occurred over other superficial tumours Amongst those investigated were secondary deposits in the breast from carcinoma of the bronchus, secondary deposits in the neck from hypernephroma, metastatic nodules in distant sites from a primary site in the breast, malignant melanomata, superficial deposits in lymphosarcoma and Hodgkin's disease, fibrosarcomata of the calf and pectoralis major muscle, carcinomata of the parotid, and secondary deposits from carcinoma of the breast and malignant melanomata in superficial lymph-nodes In all these cases there was an increased emission of infra-red rays over the swelling as compared with the surrounding skin and the normal side Some benign fibroadenomata of the breast were also " hot ", and in a few cases were indistinguishable thermometrically from carcinomata, the " hot " fibroadenomata appeared to be of the softer and more rapidly growing variety Benign nævi of the skin and one sclerosing hæmangioma were, however, of normal temperature Fibrosis, adenosis, and cysts in the breast were either of normal temperature, or occasionally, in the case of cysts, were actually 1 to 2 degrees colder than the surrounding skin and the other side There was only one exception where a cyst was " hotter ", and subsequent histological examination showed this cyst to be acutely inflamed

Skin temperatures in patients with peripheral vascular disease have also been measured by this method, and a drop in temperature over the site of a localised vascular occlusion in a limb has been observed In two cases the estimated site of the block has been confirmed by arteriography, and in two cases a below-knee amputation has been performed successfully for arteriosclerosis where the below-knee temperature appeared to demonstrate an adequate blood supply It has also been used as a rapid method of temperature measurement in assessing the effect of lumbar sympathetic block It is possible to demonstrate the site of incompetent perforating veins in varicose ulceration by means of a rise in temperature at the spot where deep venous blood is forced to the surface by the calf pump, but the method of demonstration is at present too tedious to be of clinical value It has also been observed that some varicose ulcers are hot and others cold Hæmangiomata and arteriovenous fistulæ also exhibit a raised temperature

Finally, in a small series of cases, observations have been made of the changes in temperature of superficial carcinomata during and after radiotherapy and chemotherapy

DISCUSSION

Although it must be emphasised that observations have hitherto been made on only a small number of cases, the results have been so uniform that the method seems to deserve further investigation It is clear that subcutaneous inflammatory processes and rapidly growing neoplasms, whether innocent or malignant, increase infra-red radiation from the overlying skin In an organ such as the breast, which is subcutaneous and in which distinction of degenerative from neoplastic swellings may be difficult,

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measurements of infra-red radiation may give considerable help in diagnosis It may also prove to be useful in determining gross increases or decreases in blood-supply due to vascular disease, and, in particular, may give a rapid, simple and safe method of determining the level of amputation in an ischæmic limb

At first sight, it might be supposed that infra-red thermometry was tantamount to measuring increases and decreases in blood-flow It is difficult, however, to explain in terms of vascularity alone why, in several examples of inflammation and neoplasm, skin temperatures over the lumps were found to be higher than the rectal temperatures by as much as 1 5°C A rise of temperature in an area of skin caused solely by increased transference of heat to that area by the blood-stream could not surpass that of the interior of the body Nor would a purely vascular hypothesis explain an observation made on a "hot" melanoma of a limb, in which occlusion of the blood supply led to a general cooling of the limb during the five minutes of the test, without affecting the temperature gradient between the melanoma and the surrounding skin A similar experiment conducted with a "hot" hæmangioma led to a rapid fall in the temperature-gradient between the hæmangioma and the surrounding skin and a similar rapid rise when the tourniquet was removed. It is tempting to think that local increases in temperature over lumps may on occasion be due not only to increased blood-supply but also to heat production in the lump itself—either by an increase in its metabolism, or by a decrease in the efficiency of its metabolism, which causes more heat and less energy to be produced If such a hypothesis were supported by further observations, infra-red thermometry might give a quick method of discovering whether radiation or chemotherapy was influencing a tumour

CONCLUSION

Infra-red thermometry is a method of clinical investigation which has long been neglected and warrants further study

The Schwarz thermopile was kindly lent by Messrs Hilger & Watts, and it is a pleasure to thank Mr R. Elam for his interest, and his patience in instructing us in the elements of thermal physics Without his help, and the assistance of the company, this work could not have been done We are also grateful to the clinical research committee of the Middlesex Hospital for defraying the costs of the work, and to our colleagues at the hospital for their interest and help

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FURTHER STUDIES OF THE MENSTRUAL STIMULANT

IN 1957 a new smooth-muscle stimulant was found in menstrual fluid[1] Its solubility properties put it among the group of "lipid-soluble acids" reviewed by Vogt[2] Its suggested physiological function was that, when liberated by the disintegrating endometrium early in menstruation, it passed partly into the circulating blood and thereby stimulated the myometrium to expel the decidua menstrualis, and it might also cause a temporary increase in the contractile activity of smooth muscle elsewhere Examination of the plasma of two subjects,[3] and study of the effects of the menstrual stimulant on human and guineapig myometrial preparations,[4] gave results that supported this view It was further suggested that excessive production of, or sensitivity to, the menstrual stimulant might cause primary dysmenorrhœa

We can now answer in more detail some of the further questions raised by these findings Menstrual material provided by over a hundred healthy women and six patients with primary dysmenorrhœa—representing in all about 5000 hours of menstrual flow—has been examined Details of the methods will be published elsewhere,[5] only the principal results being summarised here

NATURE OF THE MENSTRUAL STIMULANT

The menstrual extracts were previously known to contain at least two stimulant substances, differing slightly in their solubility and pharmacological properties[6] By a combination of chromatographic and other methods, *three* components of the menstrual stimulant have now been clearly separated from each other and from most of the inert material in the crude-lipid extracts of menstrual fluid Each component is itself a stimulant, or perhaps a group of stimulants so similar that they cannot yet be separated One component is notable for its ability to potentiate certain other stimulants, including, to a small extent, a second component of the menstrual stimulant These two components are acidic, and can be extracted from organic solutions by $NaHCO_3$, while the third is not. One of the acidic stimulants has some of the properties of a long-chain fatty acid, whereas the other is more soluble in polar solvents The latter is the most potent of the three components as a stimulant of uterine muscle. Among the substances that have already been described clearly enough for comparison, it most closely resembles irin, extracted from the iris,[7, 8] and prostaglandin, which originates in the seminal vesicles[9–11], but it is probably not identical with either

SPECIFICITY OF EFFECTS

The main effect is stimulation of the myometrium

When extracts containing all three components of the menstrual stimulant were injected intravascularly into anæsthetised guineapigs whose body cavities were opened under warm saline, respiration being maintained artificially, the only visible effect was stimulation of the uterus and gastrointestinal tract In vitro also, both organs were stimulated By contrast, whereas human myometrial preparations in vitro often responded very strongly, only feeble effects were seen on human gastric or intestinal muscle. This accords with the very small increase in gastrointestinal activity during menstruation[12]

Tests on other tissues and organs showed little or no effect The clotting-time of guineapig or human blood was unaffected, the blood-pressure of the anæsthetised cat was only slightly and transiently decreased[13], the beat of the perfused rabbit or

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guineapig heart was either unaffected or only slightly and transiently weakened, the permeability of the blood/aqueous and blood/cerebrospinal fluid barriers of the rabbit to *p*-aminohippurate was unaltered [14], and intramuscular injection into conscious guineapigs had no obvious effect Subcutaneous injection of 5 mg of a relatively crude extract containing all three components of the stimulant had no effect on a man, apart from causing very slight local soreness

The effects of the menstrual stimulant thus seem to have the degree of specificity appropriate to its supposed physiological function

MENSTRUAL STIMULANT AND PRIMARY DYSMENORRHŒA

It is well known that if a woman normally subject to primary dysmenorrhœa fails to ovulate in a particular cycle, the following period is often painless Artificial suppression of ovulation often has the same effect. We have not yet had the opportunity of testing for the presence of menstrual stimulant or its precursors in endometrial curettings from such cases, but it has been stated [15] that, in normal cycles, substances with the properties of the menstrual stimulant appear in the endometrium mainly after ovulation The absence of pain at the next menstrual period after an anovular cycle might well be explained by the absence of menstrual stimulant

The uterine contractions of dysmenorrhœa have been alternatively thought to be caused by vasopressin [16] Our hypothesis does not necessarily exclude such a possibility, but there is no definite evidence of any increase in vasopressin secretion during the menstrual period In one subject in whom apparently normal menstrual cycles coincided with lactation from the first month post partum,[17] the milk-ejection reflex, which is a sensitive indicator of circulating oxytocin, occurred spontaneously —i e , apart from the suckling stimulus—no more frequently during menstruation than at other times Milk ejection is accompanied by antidiuresis,[18] showing that oxytocin and vasopressin are secreted together This instance therefore does not support the theory that dysmenorrhœa is caused by vasopressin

If dysmenorrhœa is caused by excessive action of the menstrual stimulant, either an unusually large amount of it might be produced or the myometrium might be abnormally sensitive In the former case, unusually large amounts might also be found in the menstrual fluid, and in either case dysmenorrhœa would be an exaggeration of a normal process Alternatively, some different stimulant might be produced in dysmenorrhœa

In an attempt to decide between these possibilities, the subjects—all healthy students—were asked to indicate whether or not they had experienced any notable uterine pain This was recorded in 16% of eight hundred specimens, but the amount of menstrual stimulant in the 16% was not significantly different from the others Next, material was collected from five cases of severe incapacitating dysmenorrhœa Each of these specimens was matched by a normal control, as nearly as possible identical in all known variables, such as the day of the period, the duration of flow represented, and the type of absorbent material used

The amount of total lipid extracted by the usual method differed only insignificantly—5 17 mg per hour of flow in the dysmenorrhœa specimens and 4 24 mg per hour in the controls—but the stimulant potency per unit weight of lipid was half as much again in the dysmenorrhœa samples as in the controls This difference was not much greater than might be found between normal batches of specimens collected at random, but as every effort was made to *eliminate known causes of variation*, the difference may be suggestive The distribution of the stimulant potency among the various fractions of the extracts showed no difference, thus suggesting that no abnormal lipoid stimulant was present The sixth case, though presenting as dysmenorrhœa, was atypical in clinical detail and had failed to respond to treatment, and the gynæcologist suspected a psychological cause The extracts in this case about a quarter of the normal stimulant potency

ANTISPASMODICS AND THE MENSTRUAL STIMULANT

Dibutamide (ambucetamide), an antispasmodic from which some benefit has been claimed in dysmenorrhœa,[19] inhibited the effect of the menstrual stimulant on human myometrial preparations in vitro, and it also inhibited the effect of vasopressin [20]

Atropine, which is sometimes included in remedies for dysmenorrhœa but which is not generally considered a powerful agent for this purpose, had only a small inhibitory action on the menstrual stimulant in vitro

Patulin has been claimed to antagonise the stimulant actions of irin [8] and prostaglandin [11] by reason of a structural similarity, and it also inhibited the effect of the menstrual stimulant more than it did that of pitressin, but it was difficult to separate this pharmacological effect clearly from its generally toxic *effects*

δ-dodecalactone, which inhibits irin,[8] did not inhibit the menstrual stimulant

Other spasmolytics have been tested, but a specific pharmacological antagonist to the menstrual stimulant has not yet been found

SUMMARY

The menstrual stimulant, extracted from material provided by over a hundred healthy subjects, has been found to contain three clearly separable component stimulants Their principal effect in vivo is probably on the myometrium

Menstrual fluid from subjects who complained of mild dysmenorrhœa contained the same amount of menstrual stimulant as did subjects who did not complain, but fluid from five cases of severe typical primary dysmenorrhœa contained about 50% more than did control samples

Several spasmolytic and other drugs were tested and found to inhibit the effect of the stimulant in vitro to varying extents

We wish to thank Prof R A McCance for giving us every facility in the M R C Department of Experimental Medicine, Cambridge, where most of this work was done, during the tenure by V R P of a personal grant from the Medical Research Council We also wish to thank Miss J E Bottomley, Mr O Lloyd, and others for providing the myometrial samples, and for referring the severe dysmenorrhœa patients to us, Miss A Smart, A M W I , for arranging the collection of most of the specimens, others who have given invaluable help in this respect, and Dr N Ambache for gifts of irin and δ-dodecalactone

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Reviews of Books

The Viruses

Editors Sir MACFARLANE BURNET, O.M., F.R.S , director, Walter and Eliza Hall Institute of Medical Research, Melbourne, W M. STANLEY, University of California Virus Laboratory, Berkeley New York and London Academic Press 1960 Vol. 1 Pp 609 118*s* Vol 2 Pp 408 93*s*

THE three volumes, now completed, represent a vast undertaking—to present what is known of the biochemical, biological, and biophysical properties of viruses Volume 1 is concerned with general virology, volume 2 with plant and bacterial viruses, and volume 3 with animal viruses [1] Throughout, the focus is on the viruses themselves and their effects on cells, rather than viruses as agents of disease. This attitude is justified on the ground that viruses are the smallest biological units which show the characteristics of living organisms, and as such they offer a route to the understanding of living processes in biophysical and biochemical terms

Volume 1 is notable for an outstanding contribution by S S Cohen on the structural and chemical architecture of host cells, with special reference to the synthesis of polymers This is a chapter (of 188 pages) which could be read with profit by all biologists concerned with the biochemistry of cells and cell organelles It does not make easy reading but it gives a picture of the lines of future research and is therefore intensely rewarding Other valuable chapters concern the comparative chemistry of plant (H Fraenkel-Conrat), bacterial (E. A. Evans), animal (W Schäfer), and insect (G H. Bergold) viruses

Volume 2 contains many admirable chapters in which the authors have succeeded in describing their esoteric and highly specialised subjects in comprehensible terms In particular, the contributions by A Lwoff and by G S Stent on bacteriophage multiplication, C Levinthal on bacteriophage genetics, and F Jacob and E L Wollman on lysogeny are very carefully written and fully stocked with information and references Altogether, *The Viruses* is an essential reference work for any laboratory interested in virus research

A History of the Nursing Profession

BRIAN ABEL-SMITH, PH.D London Heinemann 1960 Pp 290 30*s*

DURING the past century nursing has been successively a menial and unskilled trade, an unremunerative vocation, and a profession in its own right. Many books have been written about this evolution, but for the most part they describe the role of particular individuals, or the changes in certain hospitals Dr Abel-Smith's study is probably the broadest yet published, for it surveys the antecedents of the organisation and administration of the profession in this country, and is concerned with statistics rather than personalities, Government reports rather than private diaries

Beginning with a period when Sir James Paget could pronounce the nurses at even a London teaching hospital "dull, unobservant and untaught" (though it seems that the sisters were usually "widows in reduced circumstances"), Dr Abel-Smith describes the introduction of training methods They were applied first for nurses at voluntary hospitals, and later, at poor-law infirmaries (The death, from neglect, of a pauper in Holborn Workhouse in 1864, prompted an investigation by *The Lancet* Public attention was focused on an appalling state of affairs to an extent which caused Miss Nightingale to acknowledge that she was "much obliged to that poor man for dying") Later chapters deal with the founding of the first major professional organisation, the British Nurses Association, and the battle for registration. A bill to register nurses was laid before Parliament every year from 1904 to 1914, but failed because doctors, and nurses themselves, were divided in their support of it. Not until 1919 did it pass into the statute-book.

Finally came the problems which have arisen under the National Health Service Act, and Dr Abel-Smith comments pertinently on the position of a profession which has grown up in a strange way on traditions drawn partly from the Army, partly from religious orders, and partly from public schools for girls Several nations which originally modelled the training of their nurses on the British pattern have in recent years discarded it for a new system it may be that changes are overdue in this country too

Differential Diagnosis of Yaws

W.H O Monograph Series no 45 C J HACKETT, M.D , F R.C.P , World Health Organisation, Geneva, L J A LOEWENTHAL, M.D , M R.C.P , dermatologist, General Hospital, Johannesburg Geneva W.H O London H.M Stationery Office. 1960 Pp 88 17*s* 6*d*

THIS very welcome contribution to a subject by no means always easy is to be regarded as a companion volume to Dr Hackett's *An International Nomenclature of Yaws Lesions*, which appeared in 1957 It is hardly necessary to say that this too is a first-class piece of work distinguished, as was its predecessor, by magnificent and characteristic photographs Only illustrations of diseases likely to be confused with those of yaws have been selected. Among the skin conditions which may be mistaken for yaws, those causing lesions of the palms and soles are the least understood and most troublesome

This book will appeal mostly to the field worker, especially in the later stages of an eradication campaign when the manifestations of yaws have disappeared as the result of mass penicillin treatment, for it is then that many lesions not due to yaws become prominent.

The subject matter is conveniently divided into three headings lesions likely to be confused with early yaws lesions, those likely to be confused with yaws hyperkeratosis, and those likely to be confused with late yaws lesions In the first category are impetigo contagiosa, ecthyma, scabies, chigger lesions, leprosy, tropical ulcer, lichen spinulosus, pityriasis rosea, psoriasis, mycosis, phrynoderma, drug eruptions, sickle-cell anæmia, and tuberculous dactylitis, in the second, pitting, plantar thickening and fissuring, callosities, plantar warts, and rat bites, and in the third, tropical ulcer, granuloma venereum, cutaneous tuberculosis, perforating ulcers, cutaneous leishmaniasis, blastomycosis, depigmentation, osteomyelitis, and onchocerciasis

This booklet should remain for many years the *Ultima Thule* in the differential diagnosis of yaws

A Textbook of Gynecology

LAMAN A GRAY, M.D , F.A.C.S , F A.C.O G , associate professor of obstetrics and gynecology, University of Louisville Medical School, Kentucky Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 470 124*s*

DR Gray and his publisher have combined to produce a textbook of originality and merit He has selected his material carefully and presented a clear, precise, and balanced summary of modern gynæcological practice. An attractive and lucid style never leaves his meaning in doubt

Throughout the emphasis is on a proper understanding of basic gynæcological pathology, but careful attention is paid to the mounting evidence that emotional factors can cause certain disturbances in the female genital tract Although the standard is everywhere high certain sections deserve special mention. In the opening chapter the correct relationship between gynæcologist and patient is discussed with sensitiveness and a deep understanding of women The chapter on benign and malignant conditions of the cervix is very effective. Beginning with obviously benign lesions, Dr Gray passes to an examination of pre-malignant conditions, next to carcinoma-in-situ and its cytological diagnosis, and finally to frank invasive carcinoma. The photomicrographs, black and white and colour, are well chosen In this chapter and throughout the book the photomicrographs are large enough to be seen clearly, and the colour reproduction is true. There is a comprehensive and well-balanced account of the place of hormone therapy in gynæcological practice. The chapter on diseases of the ovary is full and authoritative and again aptly and beautifully illustrated Certain common gynæcological operative techniques are described and further clarified by half-tone drawings specially prepared for the book

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[1] See *Lancet*, 1959, ii 545

At the end of each chapter are a few well-chosen references, some historical, some experimental, and some recent clinical articles, and they are drawn from the European as well as the American literature

In relation to the rest of the book a little more might have been said about prolapse and its operative treatment The section on sterility might be improved by more attention to the clinical approach and management, this chapter tends to be a catalogue of possible investigations and treatments In the treatment of uterine fibroids myomectomy is not given enough prominence

This beautifully produced book deserves inclusion in all departmental libraries as an outline for undergraduate and postgraduate teaching

Trauma in the Aged

Editor EDGAR M BICK, M D, attending orthopædic surgeon, Mount Sinai Hospital, New York New York and London McGraw-Hill 1960 Pp 524 124*s*

"WHEN youth is fallen, there's hope the young may rise but fallen age for ever hopeless lies" Thus the poet of a hundred years ago and certainly the statistics quoted in this book bear out his opinion In the United States the death-rate due to accidents is, for the population under 65, approximately 50 per 100,000 In the case of the "senior citizens" (as they are here termed) the rate is almost four times as great Those of 65 and over comprise only 8% of the United States populace, but they contribute 29% to the total number of accident deaths each year

Eighteen authors, most of them from New York hospitals, are represented in this book, which is concerned both with the general problems of old people who have been hurt, and with the management of specific injuries Some readers may wish that more articles on the general subject had been included, and that such matters as analgesics, nursing techniques and the treatment of thromboembolic complications had been considered The sections, too, which are devoted to particular injuries might have been less comprehensive but more relevant to geriatrics there is an otherwise excellent chapter on the crush syndrome, in which only two brief paragraphs are of special significance in the elderly patient

This book can be recommended as a practical and conservative exposition of those methods which are used in North America to restore to health old people who have had an accident They are very similar to those practised here if he could have foreseen their evolution, George Crabbe (who lived to be a very senior citizen indeed) would, perhaps, have recast his lines

Active Alerted Posture

W E TUCKER, F R C S, consultant orthopædic surgeon, Royal London Homœopathic Hospital Edinburgh E & S Livingstone 1960 Pp 64 10*s* 6*d* (17*s* 6*d* in de luxe edition)

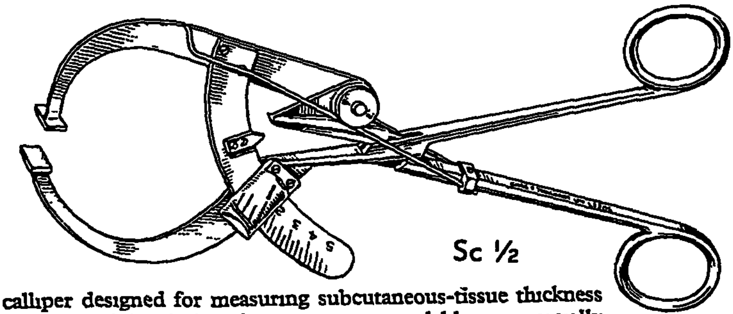
IN this monograph, by a surgeon who has often treated internationally famous athletes, many cases of arthritis, rheumatism, and disc degeneration are attributed to bad posture Sitting or standing in a slumping fashion throws, he believes, an unnatural strain on various joints which will eventually degenerate He advocates the acquisition of a habit of standing in an "active alerted position" ("top of head trying to touch the ceiling navel press-buttoned to the spine buttocks pinch-proof, and ground gripped with the toes") and claims that many physical and some emotional disorders can be prevented or cured in this way. His book is addressed to physiotherapists and trainers as well as to doctors, and is certainly much more convincing, and more easily understood, than many others which have been written on the same theme.

Rose and Carless' Manual of Surgery (19th ed London Baillière, Tindall & Cox 1960 Pp 1389 84s)—Rose and Carless is an old friend which has received a further and vigorous rejuvenation in this edition, edited by Sir Cecil Wakeley, Mr Michael Harmer, and Mr Selwyn Taylor Happily unity has been restored after its recent dichotomous two-volume adventure There has been much and excellent rewriting by the editors and their fifteen contributors May we plead for still further pruning in the next edition, beginning with the omission of the illustration of classical eponymous ligations for aneurysm, the substitution of the coloured illustration of a breast sarcoma for something more useful, and less preoccupation with syphilis (which has 46 references in the index) in exchange for greater interest in diabetes (which has 1)? In these days of high prices, this book is excellent value for money

New Inventions

FORCEPS FOR THE MEASUREMENT OF SKIN-FOLD THICKNESS

MEASUREMENTS of skin-fold thickness are being increasingly used as an index of body fat [1–3] The qualities necessary in a calliper designed for measuring subcutaneous-tissue thickness have been defined,[4] but the instruments available commercially are large and cumbersome Although they permit great accuracy of measurement they are frightening to small children The instrument described here, designed to make measurements to within 0 25 mm, is small enough to be concealed in a coat pocket With it fat thickness can be measured below the angle of the scapula in any child without causing alarm



The forceps comprises a pair of box-jointed handles, one being connected to a curved jaw which is fixed, and the other to a similar jaw which can move freely on a second hinge The faces of the jaws are rectangular (6 × 15 mm) When they are approximated by closing the handles, increasing pressure is exerted between the jaws, and this is so adjusted that, when two pointers close to the box joint of the forceps handles are in line, the force between the jaws is 900 g, as recommended by Edwards et al [4]

This instrument has been made of stainless steel to our design by Chas F Thackray, Ltd, 10, Park Street, Leeds, 1

Sheffield Region Cardiovascular Centre,
City General Hospital,
Sheffield, 5

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A B KESTERVEN

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1 Tanner, J M *Clin Sci* 1950, 9, 259
2 Hicks, D A, Hope, A, Turnbull, A C, Verel, D *ibid* 1956, 15, 557
3 Lewis, H E, Masterson, J P, Ferres, H M *ibid* 1958, 17, 369
4 Edwards, D A W, Hammond, W H, Healy, M J R, Tanner, J M, Waterhouse, B H *Brit J Nutrit* 1955, 9, 133

THE LANCET

LONDON 29 OCTOBER 1960

Government of Greater London

FIFTEEN years ago Prof PATRICK ABERCROMBIE wrote[1]

> "Give a man and his wife a first-rate house, a community, and occupations of various kinds reasonably near at hand, within a regional framework which enables them to move freely and safely about, to see their friends and enjoy the advantages of London, add to these a wide freedom of choice, and they will not grumble in the years immediately following the war"

ABERCROMBIE's plan, though not itself dealing with government, would have called for some kind of regional authority with powers of direction and fiscal control No such authority has been set up, and if in 1960 the Londoner and his wife are still grumbling, who shall blame them? The latest and most impressive approach to this problem has been made by a Royal Commission, under the chairmanship of Sir EDWIN HERBERT, which was appointed in 1957 to examine the system of local government in the Greater London area, and which has now reported[2]

The report is informed by a conviction that the people of this area lack homogeneity "There is no strong social unity within the Counties of London or Middlesex" The commissioners admit ruefully that any solution it offers is bound to arouse strong opposition from some quarter The solution it does offer is founded on two main proposals

> 1 That the primary unit of local government in the Greater London area should be the "Greater London borough" having (save for the city of London) a population of between 100,000 and 200,000
>
> 2 That an authority—the Council for Greater London—with limited functions should be established to cover the area of the proposed new boroughs

The duties of the *Greater London boroughs* of which there would be some 52, would include the following

> To receive and consider applications for planning consent within the borough area, to be the highway authority for all except main roads, with responsibility as agent for the Council for construction work on main roads, to be the housing authority within the borough boundaries, to act as education executive with day-to-day management of schools, including the school health services, in its area, to be fully responsible for the whole range of personal health, welfare, and children's care services, to undertake refuse *collection*, to supervise parks, art galleries, and museums, to operate the Food and Drugs Acts and regulations, and to control atmospheric pollution

The new boroughs would perform their functions as of right—that is, not as delegated functions—and without overlapping with or duplication by the wider Council

The duties of the *Greater London Council* would include

> Education planning and control, town and country planning as the local planning authority, housing to supplement needs not met by the boroughs and taking over existing Greater London L C C housing estates which should, where appropriate, ultimately be given to the boroughs in which the houses are sited, traffic management, highway planning and main-road construction and maintenance, ambulance services and fire services, sewerage and refuse *disposal*, and the appointments of coroners (except in the city of London)

The members of both the borough councils and the Greater London Council would be elected by direct public ballot for three years Each borough council would have about 100 members, while the Greater London Council would be constituted on the basis of one member to represent each parliamentary division The commission's revolutionary proposals would have the effect of putting out of existence the London and Middlesex county councils, "demoting" two county boroughs (East and West Ham), and annexing substantial urban parts of Essex, Kent, and Surrey

The Commission seems to have been impressed by the unhappy relations between some county authorities and local councils, which have not recovered from losing services to the county It also seems to be convinced that services provided from the town hall are bound to be better and more acceptable to the burgess than the same services provided by the local branch of the county department Where the medical officer at the town hall is also the county's area medical officer, the Commission has little use for him Throughout the report the emphasis is much more on organisation than on the quality of people working in the organisation Yet the quality of these people—and especially of the highly-trained—is a vital factor in the standard of service When this is realised better in town and county hall, and the realisation is acknowledged in improved salary scales, there may be a halt to the damaging migration from local government of engineer, architect, doctor, nurse, and psychiatric social worker

In formulating its proposals the Commission was apparently much influenced by the appalling traffic conditions on the roads, by the continuing need for new houses, by the difficulty of clerks in getting from home to office and of factory workers in securing a decent home not too far from their jobs, by the sprawl of urbanisation outwards from Central London without good really *local* government, and by the increasing needs of the increasing number of old people As regards public health, the report holds promise of improvement through the reunion of sanitation, hygiene, domiciliary health services, midwifery, health education, preventive vaccinations, "meals on wheels", provision of nursing appliances and laundry, surveillance of isolated old people, chiropody, and mental health and welfare services under one management, with the housing department next door and the home nurse a few steps away

Early in the report the Commissioners complain that good people will not come forward to be borough councillors, and they express the hope that the new scheme will revitalise local government The commission's blood-transfusion could hardly fail in time to improve the arteries and the circulation of London's local government, whether the tissues were revitalised would depend on the quality of the new blood

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[1] Abercrombie, P Greater London Plan H M Stationery Office 1945

[2] Royal Commission on Local Government in Greater London 1957-60 Cmnd. 1164 H M Stationery Office 28s 6d

Ethionamide

Isoniazid, the most potent of the anti-tuberculosis drugs so far discovered, is a derivative of isonicotinic acid Another derivative, isothionicotinamide, was synthesised in 1951 by Lee in the U S A , and in the following year by Libermann in France In-vitro studies showed that it was about 400 times less active than isoniazid on tubercle bacilli, but its in-vivo activity was considerably greater [1] [2] Unfortunately, it appeared to be totally ineffective in man [3] Further homologues were prepared by the French workers, and finally 2-ethylisothionicotinamide (ethionamide) was selected for clinical study, as it was found to be 30 times more active in vivo than the original thioamide, and no more toxic The laboratory experiments leading up to its first clinical trial have been summarised by Rist et al [4] It is active against isoniazid-resistant bacilli, and ethionamide-resistant strains are sensitive to isoniazid There is, however, a suggestion of cross-resistance between ethionamide and thiosemicarbazone, many ethionamide-resistant strains have been found resistant also to thiosemicarbazone, but strains resistant to thiosemicarbazone after in-vitro passage have been sensitive to ethionamide Ethionamide-resistant cultures have been isolated from a patient who had received large doses of thiosemicarbazone, but they have also been obtained from patients not known to have previously received either thiosemicarbazone or ethionamide. Studies of the bacterial populations in infected mice suggested that treatment with ethionamide alone would lead to the development of resistant populations, but that this could be avoided if streptomycin or isoniazid was used as well

The first clinical trials of ethionamide were started by Brouet in 1957, and in 1958 he reported his findings at a meeting of the International Union against Tuberculosis [5] The drug appeared effective in previously untreated disease in doses of 1 g a day, but strains of diminished sensitivity appeared in the sputum of some patients [6] A small group of 8 patients was treated with ethionamide plus isoniazid, after three months only 1 patient was still sputum-positive, the culture being sensitive to both drugs Hutton and Tonkin [7] treated 7 African patients who had acute pulmonary tuberculosis with 1 g of ethionamide daily in four divided doses, and 1 g of streptomycin daily for six months Of the 6 examined bacteriologically after six months, only 1 gave a positive culture, this strain was resistant to both ethionamide and streptomycin There have been several other reports of clinical experience with ethionamide, mainly from France, but they have added little to our knowledge of the value of the drug in previously untreated patients, for the trials have not been carried out in such a way that the results can be compared with those of the well-tried combinations of streptomycin, *p*-aminosalicylic acid (P A S), and isoniazid

While treatment with ethionamide alone of newly diagnosed patients who are not seriously ill is certainly defensible, there may be more doubts about the justifiability of treating acutely ill patients with this new drug together with isoniazid or streptomycin If the new one fails to protect against resistance to the other, the patient's chances of complete recovery may have been reduced In Great Britain the best available chemotherapy can be given to all who need treatment, and it could be argued that it is unjustifiable in such circumstances to treat a patient with a combination of drugs that may be less effective In countries where, owing to lack of money and facilities, only few can receive the best, such a trial might be more defensible, and if the new drug offered considerable advantages over P A S as a companion for isoniazid in large-scale treatment, the investigation could be considered fully warranted But even in these circumstances it would be warranted only if it were planned and executed in such a way that a clear answer could reasonably be expected to emerge All too often in the past, uncritical clinical experiments in chemotherapy have not only put patients needlessly at risk but have also hampered the progress of knowledge We hope that well-planned large trials of ethionamide with isoniazid or streptomycin will be carried out soon, for until these are completed the potential benefit of this new drug cannot be determined

More is known about its value in treating patients with tubercle bacilli resistant to the three main drugs In such patients there is much less ethical difficulty, for they stand to lose very little, if anything, by taking part in well-conducted trials Somner et al [8] administered tetracycline (4 g daily) as the companion drug in 7 cases of advanced disease with sputum cultures resistant to streptomycin, isoniazid, and P A S The patients received 1 g of ethionamide in two doses of 500 mg daily In 5 there was an initial effect on the bacillary content of the sputum, but ethionamide-resistant cultures then appeared, in 1 the sputum remained occasionally positive up to seventeen weeks, but resistant strains were not detected, in only 1 did the sputum become persistently negative on culture

The clinical trials committee of the research committee of the British Tuberculosis Association undertook a preliminary clinical study of ethionamide in 1959, at the request of a pharmaceutical firm They treated patients with advanced disease and cultures resistant to the three main drugs with ethionamide (0 5 g daily) and either cycloserine (0 5–1 0 g daily) or pyrazinamide (2–3 g daily)

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[1] Gardner, T S , Wenis, E , Lee, J *J org Chem* 1954, 19, 753

[2] Libermann, D , Rist, N , Grumbach, F *Bull Soc Chim biol , Paris,* 1956, 38, 231

[3] *Quart Progr Rep V A Chem Tuberc* 1955, 10, 44

[4] Rist, N , Grumbach, F , Libermann, D *Amer Rev Tuberc* 1959, 79, 1

[5] Brouet, G *Bull Un int Tuberc* 1958, 28, 228

[6] Brouet, G , Marche, J , Rist, N , Chevallier, J , Le Meur, G *Amer Rev Tuberc* 1959, 79, 6

[7] Hutton, P W , Tonkin, I M *Tubercle, Lond* 1960, 41, 253

[8] Somner, A R , Ross, J D , Macleod, H M , Stewart, S M , Horne, N W , Crofton, J W *Brit med J* 1959, i, 486

At the time of their preliminary report[9,10] 13 out of 25 patients in the pyrazinamide group had negative cultures at the end of the third month, and 8 out of 15 at the end of the sixth month, of treatment. The corresponding figures in the cycloserine group were 18 out of 21 and 7 out of 11 In the pyrazinamide group (29 patients) cultures with decreased sensitivity to pyrazinamide were isolated in 9 cases and to ethionamide in 5 cases In the cycloserine group cultures with decreased ethionamide sensitivity were found in 9 of 23 patients Sensitivity tests were done on 26 patients in the pyrazinamide group before treatment was begun. In 2 cases the strains were 4 and 8 times less sensitive to ethionamide than the standard test strain, and in 3 the strains were from 4 to 32 times less sensitive to pyrazinamide.

It seems clear that neither of the combinations used was highly effective in this type of case, although the finding that half the patients had negative cultures at six months is sufficiently promising to justify further investigation, especially as the dose of ethionamide was only half that originally used by BROUET.

This study was not devised to compare the effects of these two drug combinations, but only to gain experience of the new drug and to assess whether it was worth extended trial. Further trials now being carried out by the research committee of the British Tuberculosis Association are designed so that drug combinations can be compared, using ethionamide with cycloserine in one group and ethionamide, cycloserine, and pyrazinamide in another, with larger doses of ethionamide than in the pilot study Ethionamide is also being administered with streptomycin to patients with cultures resistant only to isoniazid and P.A.S These controlled, cooperative investigations, which take considerable time and labour, will eventually provide much information of value for treating those in whom initial treatment has failed.

Ethionamide, though a promising drug, has one important disadvantage. Many patients cannot tolerate it in more than small doses, because of anorexia, abdominal discomfort, and nausea and vomiting BROUET[5,6] reported that only 55 of 102 patients attempting to take 1 g daily had no symptoms of intolerance, 6 had transient anorexia, and 29 intense persistent anorexia, and 5 could not continue the drug at all. BROUET recommended that treatment should begin with small doses and the full dose of 1 g be reached in stages 6 of the 7 patients treated by SOMNER et al.[8] with 1 g had troublesome symptoms needing reduction of dose or temporary interruption of treatment. SOMNER[11] later carried out a controlled trial with daily doses of 0 5, 0 75, and 1 0 g daily With the smallest dose there was very little intolerance, but interruptions of treatment became commoner as the dose increased Enteric-coated tablets have been used in an effort to reduce the gastrointestinal symptoms, but there is no satisfactory evidence that they do so, and the coated tablets appear to give more variable and lower serum levels The drug has also been given rectally by suppositories, which are claimed to give rise less commonly to intolerance[12]; but symptoms of intolerance still occur with rectal administration, suggesting that the effect is not a local one on the stomach.

It should not be assumed that drug intolerance is the same the world over LAUCKNER[13] studied tolerance to ethionamide in 21 African patients in Nigeria. They received from 625 to 1250 mg daily in two doses, according to weight (approximately 15–17 mg per kg), for twelve weeks The patients were not in hospital, but attended a clinic weekly, except for 7 who missed one to four weeks' treatment for financial or domestic reasons No patient had to stop taking the drug or have the dose reduced because of symptoms of intolerance. 9 had no symptoms at all; 3 had mild, transient diarrhœa, possibly unassociated with the drug; 6 had anorexia; and 4 reported more persistent abdominal pain or vomiting Of the 7 African patients treated by HUTTON and TONKIN[7] in hospital in Uganda with 250 mg four times a day, none had any troublesome symptoms There is a suggestion therefore that tolerance to ethionamide, as to other drugs, may vary considerably between races or even between hospitals The apparently common intolerance in Europe should not prevent full investigation of the drug elsewhere. No other troublesome toxic effects have been reported. A metallic taste in the mouth may be complained of; and excessive salivation and sore mouth or tongue have been reported in Africans, improving when yeast was given.[15] Gynæcomastia appeared in 3 patients receiving ethionamide and streptomycin, receding with testosterone treatment.[7] Probably a few additional toxic reactions will be reported as the drug becomes more widely used; but on the present evidence it appears to be a safe, though often unpleasant, one to take. The mechanism by which the gastric symptoms are produced is unknown. It should be much more fully investigated, for if a way can be found to make ethionamide more tolerable it may turn out to be a valuable drug Certainly at present the evidence is insufficient to justify its use, other than in carefully controlled trials, in newly diagnosed cases of tuberculosis, and the poor tolerance of it severely limits its value in those unfortunate patients whose physicians' mistakes, or whose own lack of cooperation, have led to failures of treatment.

Professions Supplementary

As usually understood, a profession possesses (1) a body of knowledge or art, which it seeks to expand, and (2) a standard of conduct which goes beyond the performance of specific duties In one profession the knowledge or technique may be more important, in another the ethical code. Thus CARR-SAUNDERS and WILSON[14] said that in the typical profession the technique is founded on basic inquiry The work of doctors and dentists, for example, is founded on science, and demands a long specialised intellectual training On the other hand the work of nurses and midwives is founded only on the *application* of a science; and the claim of

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9 Somner, A. R. *Tubercle Lond.* 1960, 41, 309
10 Russell R. W., Stewart, S. M., Somner, A. R. *Brit. med. J* Oct. 22, 1960, p. 1207
11 Somner, A. R. *Tubercle, Lond.* 1959, 40, 457
12. Vernin P., [illegible], C., [illegible], R., Rist, N *Rev. Tuberc., Paris* 1959, 23, 454
13 Lauckner, J R. *Tubercle, Lond.* 1960 41 367
14 Carr-Saunders, A., Wilson, P A. The Professions London, 1933

these vocations to be professions is sustained by their heavy responsibilities rather than their academic learning. The nurse and midwife may not be scientists, but they certainly hold positions of trust. The present tendency of more and more groups to adopt a professional organisation can be criticised on the ground that many of them are more closely equivalent to the medieval craft than to professions as *formerly recognised*, but for our part we welcome the trend towards professionalism for two reasons. First, because people who take pride in their status always raise their standards, and, secondly, because public services staffed by members of independent professions are far more likely to thrive than services staffed by people who are primarily State employees.

This week the Royal Assent is likely to be given to an Act setting up a professional organisation for seven new "professions supplementary to medicine." Eleven years have passed since committees were set up, under the general chairmanship of Sir ZACHARY COPE, to consider what should be done, and the delay following the Cope report[15] has been due to differences of opinion about the composition and control of the professional licensing boards. This delay, however, has had at least one good effect, in that it has enabled the collective name to be changed from "medical auxiliaries" to "professions supplementary to medicine"—a happier (though still imperfect) description of a group of devoted servants of the public. Doctors know better than most the value to the community of chiropodists, dietitians, occupational therapists, physiotherapists, radiographers, and remedial gymnasts, and we join with the public and Parliament in approving the status now given to these professional colleagues. We may, however, extend a special word of welcome to that group whose work the public never see but who are in a special sense our indispensable helpers—namely, the medical laboratory technicians. They bear the brunt of routine clinical pathology, and their role in research is also important.

To all the professions supplementary to medicine, their new status is both an achievement and a challenge. Standards and traditions will have to be established and maintained, so that they may do still better what they are already doing well. Professional status should prove a step forwards as well as upwards—not only, we hope, towards proper financial and other recognition but also towards greater opportunities for service.

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[15] See *Lancet*, 1951, i, 895.

Annotations

HARVEIAN CHALLENGES

LAST week's Harveian oration was given by Sir Francis Fraser, who, like William Harvey, was physician to St Bartholomew's Hospital. Fraser's main appointment, however, was one of a new kind, and he thinks of the institution of professorial units in 1920 as a return to the Harveian way of solving biological problems by observation, experiment, and measurement. His commentary on the fifty years since he qualified ended with a highly topical appeal for a biological approach to health and disease.

Though there were several earlier examples in Germany and the United States, the first comparable opportunities for clinical research in this country we owe to the Royal Commission for University Education in London, under Lord Haldane, which recommended the appointment of professors who would give most of their time to teaching and research, working through hospital units. Because this report came out just before the first world war, no immediate action was taken, but by the end of 1921 there were in London five units in medicine and four in surgery, controlled by full-time professors or part-time directors, and outside London Cardiff had established medical and surgical units. Clinicians were now eager as never before to use any help they could get from physiologists and biochemists and their quantitative methods, and in those days it was members of the staff of the professorial units who carried out these procedures. The units in London were established just in time to apply important advances in the basic sciences, and Sir Francis regards their establishment as "the first concerted action in this country to enable clinical medicine to meet the challenge of William Harvey's great achievement by training young clinicians to be clinical scientists."

In many respects the Goodenough report in 1944 carried on from the recommendations of the Haldane Commission, and now there are only a few medical schools without a full-time professor of medicine directing a unit with full-time assistants, wards, and laboratories. The number of young clinicians trained to utilise the methods of the basic sciences is extremely gratifying, and Sir Francis puts it down to the creation and influence of the university professorial units. But there was one striking difference in the Haldane and Goodenough reports—namely, the emphasis given by the latter to social and preventive medicine and to psychiatry—two closely related subjects. There are still not nearly enough men qualified to have charge of academic departments of social medicine, and in psychiatry there is little if any basic knowledge of how emotional and mental disturbances affect physiological processes. We face also the reverse problems—the effects of illness on the social equilibrium of patients and their families and on their mental and emotional reactions.

At the conference in Chicago last year on postgraduate medical education, it was generally agreed that postgraduate education in social medicine and psychiatry would remain ineffective until undergraduates are trained to appreciate the numerous social and community factors of ill health, "and this," said Sir Francis, "will only be accomplished when the physicians and surgeons themselves set a good example by developing a biological and ecological approach to every patient under their care." Some medical schools have taken steps to introduce the undergraduate to the conditions met with in family practice, but nothing can replace the example the student should be given by all his teachers. As Lord Adrian said in his British Medical Association address of 1959, "it would be a great mistake to think that there can be a general advance without the support of every doctor who has patients to understand." General practitioners and consultants, Sir Francis concluded, are both able to contribute to this advance and to meet this new challenge, and they are more likely to do so if they cooperate both with each other and with people in public health. "Surely the senior physicians and surgeons of our general hospitals are the persons to take the lead in forming such a partnership, each for its own community. Regular meetings of representatives of the three divisions of the National Health Service, and perhaps of the clergy also, in the area would soon show how each can best help the others and how the hospital and local-authority services can utilise the peculiar experiences of family doctors to supplement their own restricted and specialised training."

RENAL BIOPSY AND AMYLOID DISEASE

IMPORTANT points about renal amyloid disease are underlined by Heptinstall and Joekes[1] in an account of 11 cases proved by renal biopsy. These cases were found in a series of 220 biopsies, and Heptinstall and Joekes question the prevalent belief that amyloid disease is now rare. There was a history of osteomyelitis in 5, of pulmonary tuberculosis in 2, of chronic bronchiectasis in 2, and of rheumatoid arthritis in 1, leaving only 1 in which a presumptive diagnosis of primary amyloidosis was made. In the 2 cases of bronchiectasis and the case of rheumatoid arthritis, the primary disease had persisted and was active when the amyloid developed. In the 2 tuberculous cases there had been no activity for three and ten years. Of the 5 osteomyelitis cases 1 had been active up to a few months before the renal amyloidosis was proved, but in the other 4 there had been no evidence of activity for eight to forty years. 1 patient, with an interval of twenty-five years, had had ulcerative colitis for two years up to a year before the renal biopsy. (Does this suggest that amyloid may complicate ulcerative colitis? Evidence of such an association is sparse, but Werther et al.[2] have collected reports of 6 cases and also record an unexpectedly high incidence in regional enteritis.) The patient with the forty-year interval had been admitted to hospital several times on account of minor illnesses, but proteinuria had not been found until some months before the renal biopsy. Heptinstall and Joekes remark that the apparent absence of proteinuria in some cases for a long time after the underlying lesions had become inactive cannot be taken as evidence against renal amyloid infiltration in this interval; possibly, once started, amyloid deposition progresses very slowly in some cases and much more rapidly in others.

Though in all cases proteinuria was found at the time of biopsy, only 4 patients had had œdema at any time, and in only 2 was this more than slight; none had been present in 2 patients with proteinuria for eight and three years. 2 patients had a much-reduced serum-albumin level, and in only 1 was the plasma-cholesterol over 300 mg. per 100 ml. On the other hand, hypertension was much commoner than in previous series: of the 11 patients, 7 had systolic blood-pressures of 150 or more mm. Hg. Heptinstall and Joekes suggest this may be due to their patients' relatively good general condition, for in previous series the patients commonly had long-standing infection.

Perhaps the most important finding was the good renal function despite the severe infiltration of the kidney, especially the glomeruli, with amyloid. In 9 of the 11 cases, every glomerulus in the biopsy specimen contained amyloid in the capillary tufts. even where the glomerular involvement was extensive the tubules were sometimes not grossly abnormal, but in 3 cases tubular damage was also severe. In 1 of these renal function was so good as to cast doubt on the validity of the renal biopsy as representing the total renal damage, but in this case three different pieces of kidney were taken at the same time and all showed the same changes. Other tests for amyloid, such as the congo-red and gum and liver biopsies, were negative in several of the cases after the onset of proteinuria, and thus renal biopsy emerges as the most certain method of making the diagnosis when the full nephrotic syndrome is not present.

Amyloid disease is a mimic[3] with many vagaries[4], and its insidiousness is again shown by this series.

THE DEVELOPING CHILD

ALTHOUGH there is now reliable information on the results of cross-sectional and serial studies of child populations, regrettably little is known about the important variables in the development of the individual child. For the study of process rather than product, longitudinal investigations of individual children are required, and Prof. Herbert Birch, in a lecture at the Maudsley Hospital on Oct. 12, described some of the findings of his current work at the Albert Einstein College of Medicine, New York.

The clash of views between geneticists and environmentalists is, he believes, being replaced by a more fruitful interest in the interaction between the biological substratum and environmental influence. He has studied the behavioural characteristics of 105 infants, mostly of middle-class, college-educated Americans—a socially homogeneous group being deliberately chosen for the better study of organismic variability. Information was sought on the child's behaviour in natural surroundings, rather than from laboratory tests. Two independent trained observers each spent a day in the household, and their reports were compared with each other and also with that from the parents. There was significant agreement between the two trained observers but still greater agreement between the separate observers and the parents. Thus, provided attention was confined to actual behaviour described and parental interpretations of this were ignored, the parents' reports were valid and reliable. From this information nine separate characteristics of behaviour could be identified in each child: activity level, rhythmicity of function or its absence, response to new stimuli (whether an "approacher" or "withdrawer"), adaptability, intensity of adaptable pattern reaction, threshold of responsiveness, quality of mood, distractability, and attention span and persistence. Comparison of item analysis with protocol analysis showed that there was negligible "halo" effect in these assessments.

Although they varied greatly from child to child, and at different ages related to different basic contents of activities, the formal characteristics remained remarkably constant in each individual child, and after two years some 90% of the children retained their original position on a three-point scale (with an 0.01 level of reliability). This remarkable stability of behaviour seems to persist even after five years, but fewer children have been studied for this period.

The effects on these characteristics of different stresses, such as parental death or separation or birth of sibs, have been studied as they occurred. Rather surprisingly little effect was found, and, although the *form* of activity may have altered, the *style* remain unchanged The long-term effects of these stresses have yet to be studied Change in the form of behaviour was greatest in the active, arrhythmic, distractable child

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[1] Heptinstall, R. H., Joekes, A. M. *Ann. rheum. Dis.* 1960, 19, 126.
[2] Werther, J. L., Schapira, A., Rubinstein, O., Janowitz, H. D. *Amer. J. Med.* 1960, 29, 416.
[3] Symmers, W. St. C. *J. clin. Path.* 1956, 9, 187.
[4] *Lancet*, 1958, i, 1378.

Professor Birch's careful and objective work has provided a valuable basis for further studies, which may give much useful information relevant to child psychiatry He has still to analyse the relation of these characteristics to the more complex psychological functions, and the clustering and interrelationship of these aspects of behaviour

MUTATIONS DUE TO CHEMICAL SUBSTANCES

THE widespread use of radioactive materials both in industry and in medicine, coupled with the development of the nuclear-power industry, has attracted attention to the potential genetic risk of exposure to ionising radiations The Medical Research Council [1] declared that the dose of man-made radiation to the general population should not grossly exceed the natural background radiation, and should be well below that capable of doubling the spontaneous-mutation rate The recommendations of the International Commission on Radiological Protection [2] embody maximum allowable doses of radiation from the point of view of preventing both somatic and genetic effects

The potential genetic effects of ionising radiations have diverted attention from other factors in the modern environment that may produce changes in the mutation-rate and hence give rise to genetic damage Alexander [3] points out that many chemicals may cause increased mutation-rates in man, and that the possible dangers have been far less scrupulously studied than have the effects of radiation Most experiments on the mutagenic effects of chemicals have been done on microorganisms, plants, and insects, and very little work has been done on mammals

The most potent mutagenic chemicals so far discovered are the highly reactive alkylating agents, such as mustard-gas and its derivatives The epoxy resins, which are used as adhesives for laminated plastic materials, can also act as alkylating agents and are highly mutagenic until they are polymerised in the adhesive Sterilisation of foods by exposure to enormous doses of ionising radiations is a new technique which may prove a very cheap and effective means of preserving food Epoxides are known to be formed in irradiated foods, and these may conceivably cause genetic change in the offspring of people regularly eating such foods Other chemicals known to have mutagenic properties are formaldehyde and some peroxides Formaldehyde is used in food preservation and in "air purifiers", and peroxides are formed in heated fats and may therefore be contained in fried foods Mutations in microorganisms have been produced by some antibiotics and hormones, and by some components of weedkillers and contraceptives

The majority of chemical substances have not been studied for possible mutagenic effects, and even for those so far found to cause mutations there is no information as to the quantities that will double the mutation-rate in man The so-called "tolerable levels" for the vapours of toxic chemical substances commonly used in industry are determined usually from the doses known to produce acute toxic effects, and only rarely from assessment of the possible long-term genetic effects Alexander thinks that some industrial "tolerable levels" of chemicals already known to be mutagenic (such as ethylene oxide and ethylene imine) would produce an incidence of genetic damage which would be completely unacceptable if produced by ionising radiations

The far greater sensitivity of the embryo than of the adult to injurious agents is well known Thus damage to a fœtus may arise from concentrations of chemicals too low to produce an apparent effect on the mother The damage in this case is due not to a genetic change but to a direct toxic effect on some of the cells in the developing embryo This type of risk tends to be overlooked in determining safe doses of potentially toxic substances to which the general public may be exposed

There is clearly a need for more research into the genetic and embryonic effects of many chemicals commonly used in the home and in industry—particularly of those used in the manufacture and preservation of food. The aim should be not only to identify substances which are mutagenic but also to estimate the magnitude of the effect and to study the uptake, distribution, and metabolism of such substances in the human body Only thus can the extent to which chemicals are causing mutations in the population be determined and preventive measures taken that are comparable with those against radiation

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[1] Hazards to Man of Nuclear and Allied Radiations H M Stationery Office, 1956

[2] Recommendations of the International Commission on Radiological Protection London, 1958

[3] Alexander, P *New Scientist*, Oct. 20, 1960, p 1073

TRIPARANOL AND CHOLESTEROL

TRIPARANOL ('MER-29') blocks the synthesis of cholesterol from its immediate precursor, 24-dehydrocholesterol or desmosterol Laboratory animals treated with triparanol have a lowered cholesterol level in the liver, kidneys, blood, and aortic wall, but the level in brain and adipose tissue is unaffected [1], desmosterol, which cannot normally be detected in mammalian liver and blood, appears in large amounts [2] Prolonged administration of triparanol to monkeys and other animals effectively lowers blood-cholesterol without serious toxicity [3]

In man, moderate reduction of blood-cholesterol can usually be achieved [4] Oaks et al [5] treated 36 patients with initial cholesterol levels above 250 mg per 100 ml After four weeks' treatment, the mean fall of cholesterol was 69 mg per 100 ml (S D 24) They obtained a maximal effect with 250 mg triparanol daily, side-effects—nausea and transient albuminuria—developed with larger doses Hollander et al [6] treated 89 patients for three to fourteen months and also found that 250 mg daily was as effective as larger doses The blood-cholesterol fell in 71 of their 89 patients, the mean fall being 45 mg per 100 ml, reduction of cholesterol was greatest in those with high initial levels Serial investigations showed no toxic effects on the blood or kidneys Bromsulphthalein retention with a slight rise of alkaline phosphatase was observed in 4 patients in the early months of treatment These tests soon reverted to normal and liver biopsies showed no evidence of liver damage 2 patients, receiving 250 mg triparanol daily, developed a rash which cleared when treatment was stopped and did not recur when treatment was restarted. The fall of cholesterol started after about a week and was greatest after four weeks The cholesterol rose to pre-treatment levels two to eight weeks after triparanol was discontinued. The total body pool of cholesterol fell during treatment. There was no evidence of adrenal depression, and there was little change in urinary 17-ketosteroid and corticosteroid levels Other workers have shown that triparanol has mild œstrogenic activity[6]

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[1] Blohm, T R., Kariya, T , Lughlin, M W *Arch Biochem Biophys* 1959, 85, 250

[2] Avigan, J , Steinberg, D , Thompson, M J , Mosettig, E *Progr Cardiovasc Dis* 1960, 2, 525

[3] King, W M *ibid* p 504

[4] Goyette, E M , Elder, J C *Amer Heart J* 1960, 60, 536

[5] Oaks, W , Lisan, P , Moyer, J M *Arch intern Med* 1959, 104, 527

[6] Hollander, W , Chobanian, A V , Wilkins, R W *J Amer med Ass* 1960, 174, 5

Kountz[7] treated 75 patients with 250 mg triparanol daily The majority showed a 15-20% fall in cholesterol over the first three months, but the level then ranged upwards over a further three months This secondary rise of cholesterol was sometimes prevented by an increase in dosage to 500 mg daily Wadell[8] found a similar secondary rise. The cholesterol levels were unaffected by triparanol in 3 of his 12 treated patients In 6 of the 9 who responded initially, the cholesterol had returned to the control value after four months' treatment.

The clinical value of triparanol in the treatment of arterial disease is still undecided. It will often produce a moderate fall in blood-cholesterol, especially if the initial level is high, but in place of cholesterol, desmosterol cumulates, and this may well be as atherogenic as o'esterol. The lowering of cholesterol may persist for ly a few months, though an increase of dosage may ntrol this secondary rise.

DRUG DOSAGE FOR INFANTS

THERE is still no unanimity as to the best method of lculating drug dosages for infants and children. ponymous rules[9,10] based on the age of the child (in ars) include the following

Cowling—Average dose × $\frac{\text{age}}{24}$

Young—Average dose × $\frac{\text{age}}{\text{age} - 12}$

Dilling—Adult dose × $\frac{\text{age}}{20}$

Bastedo—Adult dose × $\frac{\text{age} - 3}{30}$

ned's Rule for infant dosage is.

$$\text{average adult dose} \times \frac{\text{age in months}}{150}$$

nother method, which relies on the weight of the child, that of Clark

$$\text{average dose} \times \frac{\text{weight in pounds}}{150}$$

Butler and Richie[11] make a plea for the adoption of lculations based on the surface area of the infant. his method is not new, but, though generally regarded that which best defines the needs of infants and children, is not widely used. The surface-area approximates to eight (kg)$^{0.7}$—i e., two-thirds power—with a standard eviation of 8%

Butler and Richie found impressive differences in the oses of acetylsalicylic acid used in North American linics, with a range of from 200 mg to 60 mg per kg ody-weight. They considered that dosage adjustments or sulphadiazine, digitoxin, and diphenylhydantoin were ften inadequate; and that this was true also of the stimation of protein, caloric, and fluid requirements They suggest that the determination of dosage according to surface area, or weight $^{0.7}$, is both convenient and accurate.

DOES BUERGER'S DISEASE EXIST?

IN 1879 von Winiwarter[1] published his pathological findings on the vessels of a leg amputated from a male patient, and almost thirty years later Leo Buerger,[2] impressed by the occurrence of limb gangrene in young men, attempted to define the histological and clinical characteristics Since then Buerger's disease has been widely accepted as a distinct entity, although from time to time critical voices have been raised. From the clinician's viewpoint the disease is typified by thrombotic lesions, usually in small arteries but often involving veins, from the size of the tibials downwards, in men below the age of 35 The condition runs an episodic course with intervals of freedom during which a fine but rich anastomotic network is developed. The digital arteries are particularly liable to occlusion, in the hand as well as the foot, and in about a third of cases a segmental phlebitis, especially in the superficial veins, complicates the disease. As the disease progresses the resultant ischæmia may necessitate amputation of one or more limbs Less commonly the thrombotic lesions may be localised to the popliteal artery with a normal arteriographic picture above and below the block· yet, in many such cases, on follow-up the small-vessel disease attributed to thromboangiitis obliterans will have developed.

The histological basis for diagnosis is even less secure· "there is so much variation from case to case, depending upon the stage of the disease and the characteristic capriciousness of the lesions, that it is difficult to give a succinct account of the histology . . "[3] How much the classical three phases of acute arteritis, organising thrombus, and recanalisation depend, not on a specific ætiological factor, but on the cellular reactivity of small-calibre vessels in a young man is debatable.

Wessler et al.[4] now argue against regarding Buerger's disease as a separate entity They point out that in vascular clinics the frequency of the diagnosis has greatly declined over the years, and in the past eleven years at the Beth Israel Hospital no new cases of Buerger's disease have been recorded despite a sharp rise in cases of arterial obstruction due to other causes They have reviewed retrospectively 84 cases in which arterial disease of the legs developed before the age of 45 In 36 of these, heart-disease or gross atherosclerosis were present; and in this group—presumably all atherosclerotic—phlebitis was present in 62%, compared with 41% in the remainder. 35 amputations from 18 patients were available for examination. In 10 atherosclerosis was present, and in 3 systemic arterial emboli, in the remaining 5 the morphological nature of the occlusion could not be determined. It was not uncommon to find organised thrombosis without atherosclerosis in a distal artery, whereas in the proximal artery of the same limb atheromatous narrowing was evident. Section through the "normal" vessel revealed, therefore, a histological picture not unlike that said to be found in Buerger's disease. The histological data from superficial-vein biopsy were similarly unrewarding, and the inflammatory changes probably did not differ from those to be expected in, say, thrombosed varicose veins Wessler et al conclude that there is no specific histological picture characteristic of Buerger's disease, either in the arteries or in the veins, and that the condition described by Buerger is indistinguishable from atherosclerosis, systemic embolisation, or bland thrombosis in a reactive vascular system They suggest that Buerger never presented data (and they are highly critical of his reproduced histological pictures) sufficient to define a distinct morbid process, and they recommend that the term be discarded

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[7] Kountz, W B *Progr Cardiovasc. Dis.* 1960, 2, 541
[8] Wadell, W R. *Ibid.* p 597
[9] Grollman, A. Pharmacology and Therapeutics. London 1958
[10] Lynn, E. V Pharmaceutical Therapeutics. London 1929
[11] Butler, A. M., Richie, R. H. *New Engl. J Med.* 1960, 262, 903

[1] von Winiwarter, F *Arch. klin. Chir* 1879, 23, 202.
[2] Buerger, L. *Amer J med Sci.* 1908 136, 567
[3] Dible, J H. in Peripheral Vascular Disorders (edited by P Martin, R. B Lynn, J H. Dible and I Aird) Edinburgh, 1956
[4] Wessler, S, Si-Chun Ming, Gurewich, V, Freiman D G *New Engl. J Med.* 1960, 262, 1129

Most clinicians and pathologists will agree in general with these conclusions Buerger's disease is doubtless wrongly and excessively diagnosed The clinician is overimpressed by the youth and sex of the patient, and the pathologist—often limited to a vessel far from the seat of the main lesion—finds a relatively normal appearance, either with an organising thrombus or with a mild inflammatory reaction, and concurs with the suggested diagnosis Digital-artery lesions, as distinct from major arterial thromboses, are common in elderly women, but because of the age and sex we do not term these Buerger's disease phlebitis is frequently present in the history of the elderly atherosclerotic but does not influence the diagnosis It is time we escaped from the idea that limb atheroma does not develop in young men, doubtless most cases of so-called Buerger's disease are due to atherosclerosis in small reactive vessels, and follow-up shows that a notable proportion die of clearly atheromatous coronary-artery disease But can we discard altogether the concept of thromboangiitis obliterans?

ROLV GJESSING

In an annotation on depression last week we referred to a "crucial observation" by Gjessing

The death of this investigator in March of last year at the age of 72 ended a remarkable medical life

The son of a Norwegian minister, he worked first, for seven years, as a practitioner and Government medical officer in a post beyond the Arctic circle His anthropological observations among the Lapps were later published in a monograph Beginning to specialise in psychiatry, he travelled widely and spent six months in the United States, where focal infection in mental patients was then being investigated The Rockefeller Foundation helped him to equip the laboratories which he had started and organised at his own expense, and within fifteen years Dikemark Mental Hospital outside Oslo became a centre of research in the metabolism of psychosis, especially of periodic catatonia

Gjessing recognised the importance of recurrent psychotic attacks of a definite duration, separated by free intervals, for the investigation of physical changes In a special unit, clinical and laboratory methods could be applied to a small number of suitable patients—e g, intake and output, regular tests of the blood and intermediary metabolism, movements, and energy balance By his understanding approach, Gjessing made the patients themselves his most careful and devoted collaborators, and his unit became a model for other metabolic units all over the world. His wise insistence on following up a small number of well-characterised psychotics over a considerable time, comparing their conditions in excitation or stupor with the symptom-free remission, enabled him to recognise changes in the protein metabolism and nitrogen balance which he was able to correlate with disturbances in the vegetative nervous system and the patients' behaviour Subsequently he came to the conclusion that physical as well as psychological manifestations could be improved by stimulation of thyroid function thyroxine, thyroid extract, and thyrotropic hormone can, if properly applied, suppress the recurrence of psychotic attacks After his retirement, he was invited by A B Stokes to be visiting professor at Toronto University and to continue his studies of periodic psychoses

Gjessing's investigations, minute in details and comprehensive in their planning and execution, are almost all published in German[1] This and his opposition to the empiricism of much contemporary psychiatric treatment may explain the small resonance he has found so far in English-speaking countries

NOBEL PRIZEWINNERS

The 1960 Nobel prize in medicine has been awarded to two men who are widely regarded as the outstanding British biologists of the day—Sir Macfarlane Burnet, O M, F R S, director of the Walter and Eliza Hall Institute of Medical Research in Melbourne, and Prof P B Medawar, F R S, Jodrell professor of zoology and comparative medicine at University College The award is made for their discovery of acquired immunological tolerance, described as one of the greatest events in the history of immunology and the starting-point of a new era in experimental biology

The discovery stemmed from Burnet's idea of the "self-marker"—that cells "learn" to distinguish their own proteins from foreign proteins, and produce antibody to foreign proteins but not to their own Since embryonic cells do not produce antibody, Burnet suggested that this hypothesis could be tested by "deceiving" the cells To do this, a foreign protein had to be injected into the embryo early in its development, and then, according to the hypothesis, the protein might subsequently behave like one of the embryo's own proteins, so that in the adult animal injections of the foreign protein would not evoke the production of antibody At first, the experiments gave negative results, but some years after the theory was published Medawar and his colleagues carried out elegant experiments which gave just the expected results They found that mice injected during embryonic life with cells from a foreign strain of mice were able, in adult life, to tolerate grafts of skin from the foreign mice This acquired immunological tolerance has now been demonstrated for many different antigens, and the elaboration of these findings has meant radical revisions in immunological theory

Burnet is similarly renowned for his researches on viruses and for his wide ranging, at both experimental and theoretical levels, in the whole territory of biology Medawar has also made a notable contribution by his demonstration that the rejection of skin homografts is an immunological reaction, and recently the Medical Research Council announced his appointment, from 1962, as director of the National Institute for Medical Research

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Sir Clement Price Thomas has been elected president of the Medical Protection Society

The next session of the General Medical Council will open on Tuesday, Nov 22, at 2 15 P M, when Sir DAVID CAMPBELL, *the president, will deliver an address The Medical Disciplinary Committee will sit on Wednesday, Nov 23, at 10 30 A M*

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[1] Disturbances of Somatic Functions in Catatonia with Periodic Course *J ment Sci* 1938, 84, 608 Beiträge zur Kenntnis der Pathophysiologie des katatonen Stupors, *Arch Psychiat Nervenkr* 1932, 96, 319, 392, 1935, 104, 355, 1939, 109, 525 Report on 8th Congress of Scandinavian Psychiatrists, *Acta psychiat, Kbh* 1947, p 93 Beitrage zur Somatologie der periodischen Katatonie *Arch Psychiat Nervenkr* 1953, 191, 191, 220, 247, 297, 1960, 200, 350, 366

Public Health

Q FEVER IN NAVAL PERSONNEL

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Q FEVER has been recognised in this country since 1949. Laboratory investigations have revealed sporadic cases and small localised outbreaks. The disease is characterised by an acute pyrexial illness with severe headache, cough, and signs of pneumonia. Convalescence is usually uneventful, and the case-fatality rate is low. Occasionally chronic infection occurs (Evans et al. 1959, Robson and Shimmin 1959).

The present investigation was prompted by the admission of a case to this hospital in July, 1959.

The patient, a man of 41, had a history of cough, shivering, and sweating for three days. He had no headache. Radiographs of the chest showed bilateral basal bronchopneumonia. The leucocyte count was 6500 per c.mm. and the erythrocyte-sedimentation rate (Wintrobe) was 39 mm. in the first hour. Serological evidence of infection with *Rickettsia burneti* was obtained, complement-fixation tests on sera taken seven and nineteen days after the onset of illness showed titres of less than 1 in 5 and 1 in 320 respectively.

The patient had returned from a training course in Wiltshire and the Black Mountains of South Wales on July 16. It was obviously possible that other men who attended this course had also been infected, and special investigations into this unit gave the following information.

Investigations

The index case joined class 645 at a Naval establishment in Wiltshire on June 4, 1959, and was on training in the Welsh mountains in the first week in July. Since the investigation did not begin until late August only single sera were obtained from men who attended the course in the early summer. From later courses it was possible to obtain sera from men on joining and leaving the courses and again three weeks or more later.

All sera were tested in a complement-fixation test using seventy-five minutes' fixation at 37°C and antigens of seven upper respiratory viruses as previously described (Fraser and Hatch 1959). A titre of 1 in 10 or greater against *R. burneti* in the human sera was considered suggestive of recent exposure. In addition, sera from cows and sheep in the vicinity of the farm buildings used as a base in the mountains were tested against *R. burneti*.

Specimens for attempted isolation of *R. burneti* were extracted with sterile saline and inoculated into guinea-pigs in two laboratories independently. These animals were killed six weeks later and their sera tested for complement-fixing antibodies to *R. burneti*.

Findings

Each week a group of about 25 men joined an establishment in Wiltshire. After five weeks they went by road to the Black Mountains in Breconshire, where they stayed for three days before returning to Wiltshire and dispersing to other Naval units. In the mountains they used as a base a ruined farmhouse with attached farm buildings set high on the side of a valley, but walked over the mountains in groups of three to test their ability to operate in open country. They lived in the open for about thirty-six hours during this test. Sheep and cattle sheltered in the farm buildings and grazed the surrounding pastureland. Lambing and calving occurred here during the winter and spring. The products of parturition were said to have been either buried or eaten by the animals and no traces could be found. Rat infestation was noticed, but it was not considered to be heavy. Contact with these animals and their excreta during the stay was inevitable. In addition men from some groups complained of multiple insect bites mainly on the head, neck, and forearms.

618 men underwent the course between May 7 and Nov. 12. They were in the mountains between June 13 and Nov. 10.

372 men were in classes 640–653, which were in the mountains between June 13 and Sept. 8. Sera were obtained from 368 of them at times varying from three weeks to four months after leaving the training area, and table I shows their distribution of antibody titres to *R. burneti*.

There were 64 men in classes 654–656. They were in the mountains between Sept. 12 and Oct. 24. All were serologically negative four days after leaving the mountains; 62 were examined again one month or more later: 1 man in class 654 had a rise in titre to 1 in 80, and another in class 656 had a titre of 1 in 10.

In classes 657–663, which followed, there were 182 men. All were bled on joining and leaving the training unit in Wiltshire and all were negative, although 1 man had unchanging titres of 1 in 10 in both sera and is not included in the totals. Further sera were obtained from 177 of them one month or more later, when 1 had gained a titre of 1 in 10.

Sera were tested from 83 members of the staff of the training centre in November: 2 had a titre of 1 in 10, another had a titre of 1 in 40. This last man had been in the mountains frequently and had had an influenza-like illness in August. The other 2 had not been in the

TABLE I—DISTRIBUTION OF ANTIBODY TITRES IN SINGLE SERA OBTAINED FROM MEN THREE WEEKS OR MORE AFTER LEAVING TRAINING CENTRE

Class no.	Period at training centre (1959)	< 1/10	1/10	1/16	1/20	1/40	1/80	1/160	1/320	No. in class	No. tested	No. positive
640	May 7 to June 18	30								31	30	0
641, 642	May 14 to June 25	38	1				1			40	40	2 (5%)
643	May 21 to July 2	27	1		1					30	29	2 (7%)
644	May 28 to July 9	28								29	28	0
645	June 4 to July 16	11	3	2		3	3	3	3	28	28	17 (61%)
646	June 11 to July 23	17	2		3	4	4	1	1	32	32	15 (47%)
647	June 18 to July 30	26			1	1	1		1	30	29	4 (14%)
648	June 25 to Aug. 6	24				1	2			27	27	3 (11%)
649, 650	July 2 to Aug. 27	45		2	1	1	2			51	51	6 (12%)
651	July 9 to Sept. 3	25			1			1		27	27	2 (7%)
652, 653	July 16 to Sept. 10	47								47	47	0

TABLE II—DISTRIBUTION OF ANTIBODY CHANGES IN 50 SEROLOGICALLY POSITIVE CASES TESTED THREE MONTHS AFTER DIAGNOSIS

Unchanged	2-fold fall	4-fold fall	8-fold or greater fall	2-fold rise	4-fold rise	Total
11	19	9	8	2	1	50

mountains but handled bedding and clothing returning from Wales.

There were 57 serologically positive cases in all. Of the 55 men who had been to the mountains, 39 had had no illness after they had left. The other 18 (36%) were ill within two weeks of leaving the centre—i.e., within about sixteen days of leaving the mountains: 2 had pneumonia, 1 had jaundice with high fever, and 15 had an influenza-like illness with fever, cough, headache, shivering, sweating, and general malaise. Radiological examinations of the chests of 53 of these men, two weeks after diagnosis, were negative.

Further specimens of serum were examined from 50 of the positive cases about three months after the initial diagnosis had been made. Table II shows the distribution of the changes in antibody titres in these men. 10 men had no detectable antibody in the follow-up specimen of serum, in 1 the titre had fallen from 1 in 320 to zero, and in 9 from 1 in 80 or less to zero.

No evidence of *R. burneti* was found in samples of dust taken by vacuum cleaner from clothing and bedding or in samples of litter from the farm buildings. None of the animals tested had antibody to *R. burneti*.

Discussion

Since the recognition of Q fever in this country (Stoker 1949, MacCallum et al. 1949), small outbreaks have been reported from most parts of England and Wales (Marmion and Stoker 1958). As might be expected in a disease normally affecting cattle and sheep, most cases have occurred in persons in contact with these animals.

It has been shown that about 5% of the herds of cattle and about 3% of the flocks of sheep in South Wales are infected, but only about 0.6% of the cases of abacterial pneumonia in the area are due to Q fever (Evans 1956).

Q fever was of considerable military importance in Italy from 1943–45. Robbins et al. (1946) investigated an outbreak there and found that 269 of a battalion of 900 men were admitted to hospital from this cause in one three-week period.

Since the present investigation began several weeks after the peak incidence of infections, some of the positive titres which were found may have been present before the men joined the training centre. However, of 182 men examined on joining the centre after the peak incidence, only 1 had a titre of 1 in 10 or greater. During 1958 and 1959, of 1323 patients with upper respiratory infections who were admitted to this hospital, and over 2000 recruits from all over this country, considerably less than 1% had demonstrable antibody to *R. burneti*. There was no evidence of an increase in the number of the civil and Naval populations in South Hampshire who had antibody to *R. burneti* during the period of investigation, yet in many of the positive cases the men had been sent on the course from ships and establishments in this area.

R. burneti was not found in dust obtained from the men's clothing or the litter in the barns in Wales. Inspection of the premises showed that men living in the farmhouse must have been exposed to large quantities of dusty litter which was heavily contaminated with animal excreta. In addition the cattle and sheep which were known to have used these barns and to have been in contact with the men were shown to be free from Q fever.

The men walked over country grazed by flocks of sheep which were known to have been infected in previous years. The men travelled along sheep tracks on the limestone or sandstone hillsides, which were contaminated with animal excreta. Since there was no rain in the area from about the middle of May to the beginning of August, these tracks were dusty. Inhalation of some of this potentially infected dust was inevitable, particularly during rest periods when the men were sitting or lying down.

Lambing in the area was almost completed by April, but a few lambs were born in May. Although no products of parturition were seen by the class leaders who were in the area in June and July, it is possible that, because of the dry weather, dust derived from the afterbirths of late-lambing ewes could have caused infection in the men.

On the other hand it is difficult to account on this basis for the large increase in cases in the latter half of July. It seems more likely that one or more new factors developed, or an existing factor increased, temporarily during this period. There is no evidence to clarify this point other than the history of numerous insect bites sustained by the men during this period.

The evidence suggests that most of the infections occurred in the latter half of July, probably in the Black Mountains, but the method of infection has not been demonstrated. The men were dispersed two to three days after the course and there was no evidence of further outbreaks, although 1 further case of Q fever occurred in each of 2 establishments to which a patient returned; these further patients had not undergone the course.

Since ticks were not seen, and the men wore boots, gaiters, and denim trousers during training, ticks were probably not the vector.

It is unlikely that these men developed chronic rickettsæmia, since at examination some three months after infection they were well and in most instances their titres to *R. burneti* had fallen. About two-thirds had diminished antibody titres, about a quarter had unchanged titres, and 3 (6%) had slight rises in titre. 16 of 18 clinically positive cases had antibody three months after the illness.

There is a similarity between these findings and those of Holland et al. (1960), who investigated Q fever in R.A.F. personnel. Since in each of the two series the proportion of asymptomatic serologically positive cases was high, the possibility exists of case-to-case spread between men in close contact with each other under field conditions. In view of the findings of Evans and Baird (1959) the history of insect bites may have some significance, but there is insufficient evidence to determine their role in this outbreak.

Summary

A patient admitted to hospital in July, 1959, was found to have Q fever. Studies on 618 Naval personnel from a training course in Wiltshire and South Wales which this patient had attended showed that 54 men had antibody to *R. burneti* and that over half of 28 men in his particular class had been infected. 3 additional cases were also detected in the staff of the training base.

Most of the infections occurred in the last two weeks of July. The evidence suggests that infection took place in the Black Mountains of Breconshire, but the mode of infection was not found.

Examination of 50 men three months after diagnosis showed no evidence of chronic rickettsæmia, although 3 had slight increase of antibody to *R. burneti*.

We thank the Medical Director General of the Navy for permission to publish, Prof. A. Bradford Hill for statistical advice, Surgeon Rear Admiral G. Phillips and Dr K. E. A. Hughes, director, Public Health Laboratory, Portsmouth, for their advice and encouragement throughout, the medical officers of the Royal Navy for their assistance in supplying information and serum samples without which this investigation would have been impossible, Dr P. V. Pritchard, medical officer of health for Gosport, for his interest in the index case, Surgeon Captain J. H. Nicolson, R.N., who afforded us all facilities in his area, the medical officers of health and the directors of the Public Health Laboratories in the areas concerned for their cooperation, and Mr E. H. O'Connor, A.I.M.L.T., for his technical assistance.

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The Widdicombe File

LXV.—"PLUCKED FROM THE BURNING"

DEAR WHIDDON,

Jan wanted me to slip over and see his son at Witherbridge. As you'll know, he's out of danger now. I suppose a fractured femur, ruptured gut, and a few burns are not really a very high price to pay for wrapping that sports car round a tree at 85 m.p.h. Thank God nobody was in the way. The local boys did a wonderful job, they're slick on accidents and my second opinion couldn't add much.

Jim was certainly lucky in choosing his spot, for the chaps at Witherbridge had him transfused and on the table within an hour. I reckon that if his track-rod had chosen to snap half an hour before it did, there would have been a good three-quarter-hour journey by the Milvercombe ambulance, with a ten-minute delay on Suffering Hill where the road's up, plus any amount of time in getting to the telephone in the first place. St. Ethelred's is quite good of its sort, but the casualty officer hasn't had much experience and finds conversation difficult except in Tamil, though they're lucky to have him, for the job was unfilled for a couple of months.

If Jim had arrived there, a cubicle would have been quickly cleared of a patient with multiple boils and another with athlete's foot, and those two old porters would have done their best to heave him off the stretcher on to a couch. It's usually possible to trace the Egyptian R.S.O. within 20 minutes (there's still no call-system you know) but he wouldn't have been able to do much except call the surgeon from one of the other hospitals and order blood. The consultant, when he got away from the advanced carcinoma he was trying to remove, would have found shifting dullness and things and ordered immediate operation, though being a general man he wouldn't have liked plating that femur. Still, Sister would take about half an hour to get the theatre ready, and by then maybe an orthopod could have been found. The moves from couch to trolley and trolley to operating-table wouldn't have helped, not to mention the trip down to X-ray, a couple of hundred yards away.

Jim needed arterial transfusion with assisted respiration and quite a lot of tissue grafting, which called for resources and personnel of a very high order. St. Ethelred's, I'm afraid, has neither. So I might easily have been writing a letter of condolence, instead of this fairly cheerful one to you. (So I might, in point of fact, if he'd been brought to my own hospital.)

Would it help, do you think, if we started calling the motor-car Captain of the Men of Death? Both the Industry and the Government seem *incredibly* oblivious of the enormous suffering that surrounds us. If anyone were seriously interested in prevention, then safety-design in roads and cars, an overall speed-limit, and a ban on high-powered motor-bikes for youngsters seem obvious, and then there's liquor, and why not make seat-harness compulsory on Motorways? Punishment for the delinquent driver should become realistic, and not just the present meaningless penny-penances and vague warnings.

Still, some accidents are bound to happen, even if we return to stage-coaches. What do you think we ought to be doing on the medical side to halt the rising tide of death and disablement? What, for that matter, is your own ex-teaching hospital saying or doing? Some have whole-time accident surgeons on a 24-hour service, though mine, I regret to admit, has *no* consultants working no time, and lots of departments are manned at night only by a reluctant H.S. or H.P., heavy-lidded from a hard day's work. Obviously we can't have the Witherbridge sort of accident team in every hospital, but we could have more of them. Some people want 25 or so centres to cover the whole country, and it sounds sense to me, though probably far too few. Probably you have views on staffing, but I hope you'll agree anyway that the centres need to be specially designed, in or near a large and efficient general hospital with ambulances (and helicopters?) going straight to them.

All this seems so obvious and desirable and important that I suppose it's quite impossible, and that's what it does in fact seem to be when one puts it to one's colleagues. "What, close our Casualty?" they say, "what a blow to our prestige. G.P.s won't send us cases, and how will Matron train the nurses?" General and orthopædic surgeons get at each other's throats, and the whole affair gets bogged down in petty politics and silly jealousies. I suppose it's hard to expect cooperation between adjoining hospitals whose senior staff haven't recognised each other's existence since 1893. But eventually, if we don't do something effective, the Ministry will decree a Central Plan of some kind—and not before time perhaps. We all know now—thanks to the independent Nuffield set-up—just how bad some old casualty departments are and how little thought sometimes goes into the planning even of new ones. No doubt you know, too, that a confusion of committees has been set up to look into this and that. Make life safer for Jim's children maybe. But the best hope (as I think has happened in two, or perhaps three regions) is for the local men themselves, and the S.A.M.O., to take a long hard look around.

Accident surgery has been remarkably neglected compared with things like plastics and chests, though the people it works on could hardly be of greater value to society. It's funny, too, that most of the chaps who are trying to do something about it seem to be near-descendants of those Colonial pioneers who lately made our great Dominions what they are. Maybe it takes an outsider to see where we fall short.

As ever,

P. C.

Conferences

GREAT ISSUES OF CONSCIENCE IN MODERN MEDICINE

FROM A CORRESPONDENT

Dartmouth College in New Hampshire, which boasts the third oldest medical school to be in continuous operation in the United States, staged a convocation on this topic on Sept. 8–10 To discuss these issues the following were asked·

René Dubos, bacteriologist and member of the Rockefeller Institute, Mahomedali Currim Chagla, laywer, India's Ambassador to the United States and Mexico, Brock Chisholm, Canadian physician, director-general of the World Health Organisation from 1948 to 1953, Ward Darley, executive director of the Association of American Colleges, Ralph Gerard, director of laboratories at the Mental Health Research Institute, University of Michigan, Aldous Huxley, novelist and essayist, George Kistiakowsky, Harvard professor and special assistant to President Eisenhower for science and technology, J H Muller, Indiana University, Nobel laureate for his work on genetics, Walsh McDermott, professor of public health, Cornell University, Wilder Penfield, director, Montreal Neurological Institute, Sir George Pickering, regius professor of medicine, Oxford University, Sandor Rado, dean and professor of psychiatry, New York School of Psychiatry, Sir Charles Snow, physicist and novelist, and Warren Weaver, vice-president of the Sloan Foundation and former vice-president of the Rockefeller Foundation

Pollution

Dr DUBOS pointed out that science is not concerned with moral or ethical issues It teaches how to do, not what to do In general it is society at large that decides what to do Dubos recalled that Hermann Biggs, a former commissioner of health for New York State, had written "Public Health is purchasable Within natural limitations any community can determine its own death-rate" He said

"The origin of the most important air pollutants is well known Depending upon the locality, they comprise the products arising from incomplete combustion of organic matter, the various chemicals released from the smokestacks of industry, the exhausts of motor-cars, the catalytic oxidising effect of solar radiation on nitrogen oxide and olefins, and mixtures of all these factors Without the need of any further investigation, it is clear that certain courses of action would go far toward minimising the medical problem caused by air pollution To improve the design of combustion equipment and of gasoline engines, to increase the height of smokestacks, to re-route automobile traffic, to displace certain industries, &c, are steps compatible with technical knowledge and which would either eliminate air pollutants or discharge them in areas where they would not constitute threats to human health But these steps could be taken only at the cost of disturbing the economic structure of the community, and of creating inconveniences for almost every one of its members

"In reality, then, the problem of air-pollution control is not only scientific in nature, but even more one to be formulated on the basis of certain human values difficult to express in terms of factual information How much of economic prosperity and of convenience of life is society willing to sacrifice to prevent lung cancers, emphysema, and chronic bronchitis that will become apparent only in the future? How can we balance the value of human suffering that will occur in some undetermined future against the effectiveness of the social performance of a community today?"

MCDERMOTT told the story of the guest in the country house who, having asked his hosts what they did with garbage, received the reply, "Oh, we just kick it around till it gets lost" He thought our attitude to air pollution had been the same, and in fairness to our children we must now tackle it seriously

Perhaps the most serious pollution problem is that of radioactive material, which, as DUBOS said, must always be a hazard, particularly to the workers, if atomic energy is to be used for peaceful purposes PICKERING remarked that contamination through tests of atomic weapons was not the really serious issue, since these tests were deliberately performed in centres of minimal population density What was serious was what lay behind them Natural defence was, of course, two-sided It should be plainly stated that war was the greatest threat to mankind, and that war was the most devastating disease the world was ever likely to know

Man's Biological Future

The future course of world population and its social and political consequences were considered by the Indian Ambassador and Aldous Huxley The AMBASSADOR made a moving speech dealing with the serious situation developing in India and appealing for help not in wealth but in "know-how" Here are some extracts

"The great crisis of this decade is not one of differing ideologies The great enemy and the threatening menace that we have to face is not Communism The really explosive factor is poverty

"At one time a rising population did not present a serious problem to India There were always epidemics, or local wars, or a heavy infant mortality and a low expectancy of life to counterbalance the large number of births I may also point out that people in those days looked upon a large number of children as an insurance—so few survived that a large family seemed to be essential But all that has changed now Advance in medical knowledge, steps taken to improve standards of hygiene, have eliminated many diseases in India which took a heavy toll of lives There are no epidemics now, and if one breaks out it can be immediately put down Civilisation no longer believes in small local wars—we have to wait for a nuclear holocaust The result has been a sharp fall in the death-rate But the birth-rate has remained the same So in a sense we have been suffering from the civilising effects of science and medical research Civilisation has shown us how to reduce our death-rate but so far has failed to point the way to a controlled population I think this is one of the most important issues of conscience in modern medicine Medicine must advance on both the fronts If it considers life is sacred and everything must be done to prolong it, it must also prevent human beings being born into an existence of poverty, destitution, and frustration The sanctity of life demands that the dignity of the individual must be upheld What dignity will millions of children have who are being born today?"

"I should like to say a word about the ethical or moral aspects of the problem To my mind morality consists in giving the least pain to fellow human beings and contributing to the largest extent to their well-being This is not, I fully appreciate, a philosophic definition of morality But it is a pragmatic one and can serve as as good a guide to human conduct as any other Applying this test, I think you are causing more misery and suffering to untold millions by denyihg a knowledge of birth-control technique than by doing everything possible to bring home to the people in this country the vital urgency of the problem of population explosion that is facing the world Nor am I impressed by the argument that it is morally wrong to take life—that we should trust to a benign and benevolent providence to feed all the mouths that exist in this world Experience, unfortunately, does not prove that all mouths are in fact fed. Millions in Asia and Africa go hungry and underfed. I would rather prevent life than bring into existence children who do not and cannot live as human beings and who are a shame and a scandal both to providence and to man."

"You might well ask me what India herself has done toward the solution of this tremendous problem that faces her. We are one of the very few Governments in the world who have officially adopted a policy of birth-control and family planning. It is not easy for any Government to do this. There are orthodox people in every religion who are opposed in principle, whatever the principle may be, to birth-control. Religions in India are no exception to this. But our Government has placed the welfare of its people before religious sentiments, and, even at the risk of offending these, has set up clinics in various parts of India to propagate extensive knowledge about birth-control and distribute contraceptives free of any cost. We have about 1800 such clinics now and by the end of our next five-year plan—in five years' time—we hope to have about 8200. I agree that this is merely the fringe of the problem."

This speech deeply impressed the meeting, as did that of Aldous Huxley, who asked what were the humane and natural substitutes for Nature's method of dealing with over-population—namely, famine, pestilence, and, in human societies, war. First, we can increase production of food and industrial goods. This is feasible, but in the long run increase of population if unchecked will outrun increase in production. Thus when the high dam at Aswan is completed the population of Egypt will have increased to a point where the newly irrigated land will not suffice to feed it. Consequently efforts to increase production must go hand-in-hand with efforts to bring birth-rates into balance with death-rates. Unfortunately death control is easy and cheap, birth-control is expensive and difficult. Though a rational population policy, internationally agreed upon, would not bring an immediate solution to our problems, it must nevertheless be adopted. If it is not, our grandchildren and greatgrandchildren will be in for the worst time of trouble ever faced by the human race. Increasing quantity will result in deteriorating quality of living, and most of the world will sink into abysmal squalor and chronic warfare.

Perhaps the most astonishing feature of the convocation was the fierce disagreement with these views expressed by McDermott and Dubos. Both doubted whether medical science had had much to do with increasing world population or whether this would be a serious problem. McDermott thought ancient Rome was probably as sanitary as modern Calcutta. Dubos, after Chagla and Huxley had spoken, thought it significant that the two experts on infectious diseases should be in opposition to the rest of the group. To your reviewer it seems astonishing and rather tragic that scientists can be so prejudiced. Has modern medical science been entirely without influence on such great epidemic diseases of the past as malaria, typhus, plague, and smallpox?

Other Topics

The remaining issues produced neither such highlights nor such controversy. The problem of the extent to which doctors should go to keep senile or suffering patients alive was raised but not fully discussed. It was agreed that if society wants euthanasia, it should not ask doctors to carry out its instructions but should license people specially for the purpose.

The extent to which we should try to improve the quality of mankind by employing genetic knowledge and the practices so successfully used in breeding cattle and racehorses received no satisfactory answer. Muller thought that, to prevent the serious genetic consequences of radiation, all men at present living might have their sperm stored in refrigerated underground tanks. Dubos thought this was perhaps the oddest legacy one generation could leave to the next.

The session on factors influencing the mind dealt largely with brain-mind relationships and with current views of the nature of conscience. The psychiatrists agreed that unrestricted permissiveness was unjustifiable and was now "out." The practice of "brain washing" was unfortunately not discussed.

Your correspondent and the two thousand others attending the convocation undoubtedly found it stimulating. Though no issues of conscience were settled, they became more sharply defined.

GASTRIC SECRETION

FROM A CORRESPONDENT

On Oct. 15 a symposium on Gastric Secretion was held at the Western General Hospital, Edinburgh, under the auspices of the Postgraduate Board for Medicine. The participants included representatives of the disciplines of anatomy, physiology, pharmacology, endocrinology, medicine, and surgery.

G. M. Wyburn (Glasgow) discussed the structure of the parietal cell as seen with the electron microscope—a technique that brings almost a new dimension into our understanding. The day may not be too far distant when enzyme arrays become anatomical actualities.

The problem of determining from the composition of mixed gastric secretion its original constituents was discusssed by E. Blair and A. A. Harper (Newcastle), J. N. Hunt (London), and A. H. James (Cardiff). The assumptions that have to be made in such inference were clearly underlined and also the dangers in the extrapolation of data that is necessary. It is still uncertain that stimuli to the parietal cells to produce hydrochloric acid always work through the intermediate release of histamine. H. M. Adam and H. Main (Edinburgh) produced evidence further supporting this hypothesis, but in another communication H. M. Adam and W. T. Irvine (London) described their failure to detect any rise in histamine in the venous effluent from the dog's stomach following stimulation of secretion.

W. Sircus (Edinburgh) described the biphasic pattern of gastric secretion in dogs following the induction of hypoglycæmia and summarised the results of experiments designed to elucidate these changes. A. W. Kay (Sheffield) discussed the possible explanations for the much lower response of the human stomach to injected histamine after vagotomy.

Hilda Tracy (Liverpool) discussed some of the properties of gastrin and the response to gastrin injections in a human subject.

R. A. Gregory (Liverpool) reviewed enterogastrone as an inhibitor of gastric secretion. He concluded that fat in the duodenum acted by inhibiting the release of gastrin from the antrum.

The drama of the Zollinger-Ellison syndrome has excited the attention of clinicians and physiologists for some years and B. G. Alton (Dublin) described an admirably documented case which included a study of the effects of acid in the small intestine on fat absorption.

G. P. Crean (Edinburgh) showed, in a careful study, the effect of hypophysectomy in reducing the parietal-cell populations of the rat's stomach, while R. B. Welbourn (Belfast) produced evidence that the effect of cortisone in potentiating gastric secretory responses might be exerted through an increase in the number of secreting cells.

The ability of long-continued oral administration of an adrenal inhibitor to decrease gastric secretion in dogs was shown by A P M **Forrest** (Glasgow)

The gastric secretion of blood-group substances and their quantitative measurement was described by D A **Price Evans** (Liverpool), the mystery of their relation to the incidence of ulcer and indeed of the significance of their presence in the gastric juice remains unsolved

D H **Friedlander** (Edinburgh) showed how the efficacy of antacid therapy could be related to the secretory capacity of the stomach

Medicine and the Law

A Draft Suicide Bill

Possible changes in the law of suicide are foreshadowed by a report from the Criminal Law Revision Committee published last week [1]

Throughout the centuries suicide in England (though not in Scotland) has been a criminal offence as well as an ecclesiastical sin. Attempted suicide has been recognised by the courts as a crime since 1845, although today the police prosecute only where there is some definite circumstance calling for punishment or where an order of the court seems the only chance of securing help for a person too weak to stand alone [2] " A severe lecture on their stupidity is mostly delivered to the offenders by a senior officer who has already satisfied himself he can hand over their future well-being to relatives or friends willing to look after them "[3]

If suicide is an offence, it must also be an offence to aid or counsel anyone to commit or attempt suicide Indeed, the English law is that the person who does so is punishable as an accessory to murder, except that in the case of suicide pacts the offence is reduced to manslaughter by the Homicide Act, 1957

The Criminal Law Revision Committee was not asked to consider whether changes in the law would be desirable It was told in November, 1959, that the Home Secretary was considering whether legislation should be introduced to provide that suicide and attempted suicide should no longer be criminal offences The committee was asked to consider what consequential amendments in the criminal law would be necessary on the assumption that it should continue to be an offence to incite or assist another person to kill or attempt to kill himself

The report is therefore entirely concerned with the legal problems which would be involved The main proposal is for a new statutory offence of aiding, abetting, counselling, or procuring the suicide of another or an attempt by another to commit suicide, for this a maximum punishment of 14 years is proposed, the court being left free within this maximum to adjust the penalty to the circumstances of each case This proposal is said to be broadly similar to suggestions put forward by the Criminal Code Bill Commission (1879), the Royal Commission on Capital Punishment (1953), and a committee of the Church Assembly Board for Social Responsibility (1959)

Included in the report is the draft of a Bill to abrogate the offences of suicide and attempted suicide, and to give effect to the committee's recommendations

It remains to be seen what changes would follow in the practice of coroners' courts The verdict that the deceased committed suicide whilst the balance of his mind was disturbed was introduced to prevent legal consequences which have long since ceased to apply. But this form of verdict is still relevant for life-assurance policies and for the burial laws of the Church of England

Court Orders Transfusion

Some months ago the Sheffield Regional Hospital Board caused some controversy by announcing that it had set up machinery for dealing with cases where a parent refused permission for a blood-transfusion to a child, under these arrangements, the local magistrates would be called to the hospital and asked to make an order under the Children and Young Persons Act committing the child to the care of a fit person [1]

At Cambridge last week the magistrates sat at a local maternity hospital to deal with the case of a newborn baby suffering apparently from a rhesus-negative condition The father, a member of the Jehovah's Witnesses, had refused permission for a blood-transfusion on religious grounds The court made an order committing the child to the care of officials of the county council's children's department, who authorised the operation The chairman of the court said " It is a magistrate's duty to protect the life of the child "[2] According to one press report, the operation was performed within an hour or so of the birth It would seem therefore that the father's attitude was known and the arrangements for the court to meet were made before the birth

This is apparently the first occasion on which this procedure has been used in order to secure legal authority for an operation in opposition to the parents' wishes Since the risk of a prosecution for manslaughter has proved no deterrent in such cases,[3] it would seem right that some such legal procedure should be available where there is a clear risk to a child's life or health But the Children and Young Persons Act was obviously intended for quite different circumstances, and there is some doubt as to whether it can lawfully be used for sanctioning medical or surgical treatment The Cambridge authorities acted reasonably in the circumstances, but it would be preferable to have specific legislation for this type of case

Death Associated with Thorotrast

At an inquest in Manchester on Oct 19, the city coroner, Mr Donald Summerfield, recorded a verdict of death from war injuries on a 37-year-old man who had died in Manchester Royal Infirmary It was stated that his skull was fractured in 1943 in an accident while he was serving in the Royal Tank Corps

Dr Alexander Nicol said in evidence that at that time 'Thorotrast' had been injected intravenously for radiographic examination, and, according to then-existing knowledge, it had been properly administered At necropsy he found that œsophageal varices had caused fatal hæmorrhage, and that the condition had been set up by cirrhosis of the liver " In the man's liver I found a deposit of the substance, and over the years it had led to the disease which resulted in his death " Dr Nicol added that since 1950 it had been accepted that thorotrast could cause cirrhosis of the liver, and its use for X-ray purposes had been discontinued

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[1] Criminal Law Revision Committee second report (Suicide) H M Stationery Office 9*d*

[2] Williams, G *The Sanctity of Life and the Criminal Law* London, 1958

[3] Wyles, L A Woman at Scotland Yard London, 1952 Cited by G Williams (footnote 2)

[1] See *Lancet*, 1960, i, 687

[2] *Times*, Oct 21, 1960, *East Anglian Times*, Oct 21, 1960

[3] See *Lancet*, 1958, i, 583

In England Now

A Running Commentary by Peripatetic Correspondents

It seems to be about as difficult for a word to gain formal admission to the French language as it was, in Biblical times, for a rich man to enter the Kingdom of Heaven, it has to be put up for discussion, debated, defined, and distinguished from existing rivals under the august arbitration of the Académie française, and even after this ordeal some weeks or even months must elapse before its *réception solennelle* Needless to say, and most happily for the continued survival of the language, none of this has the slightest effect upon the usage of the word by the public or even, I dare say, by the members of the Académie themselves The most unexpected words have a spontaneous vitality of their own.

Take, for instance, the Word of the Year, "cybernetics" This must be one of the few really indispensable pieces of semantic equipment for the traveller abroad in 1960, and it has already entered into the French that Frenchmen speak. Readers of *Zazie dans le Metro* will recall that at one point Gabriel, the sweet-smelling male *danseuse de charme* who rashly takes temporary charge of the unspeakably precocious Zazie, telephones Charles at the *bistro* Charles, glass in hand, is trying to persuade the barmaid Mado-petits-pieds to marry him when she answers the phone. He fights a superbly negative delaying action (all those who have experienced French bureaucracy will know exactly what I mean) until his beaujolais is finished and then, "arrachant l'appareil des mains de sa peut-être future, il profère ce mot cybernétique Allô"

You see? It has become a part of life.

* * *

I am not much of an archæologist, but each summer when we go to the Highlands I follow the advice of the guide-books and visit whatever may be worth seeing in the locality This year we went for the first time to Knapdale, and found it delightful. We chose our caravan site, on grounds that were mainly scenic, on an old road that wound its way through birch woods by the sea. The first thing, as usual, was to find a good supply of water I wandered off to a nearby glade, which proved to have a nice fresh stream. It also had a cave in the rocks, which I idly entered. To my astonishment, this turned out to be St. Columba's first chapel in Scotland—or so says local tradition, which has often been shown to be correct about such matters This first cell, Columba believed, was out of sight of his beloved Ireland, thus fulfilling his vow of banishment. There is an altar, a pulpit, a holy-water pool, and on the wall of the cave there is imprinted a cross The pulpit, of natural rock, is at the entrance to the cave but so related to the roof that the speaker's voice is thrown out into the glade A second cave may have been a dormitory A fascinating place in every way, with a distinctive atmosphere to it. Poor Columba —that man of many vicissitudes—must have been sad to discover, one clear day, that he could in fact see Ireland on the horizon, so that he had to move on to Oronsay and eventually to Iona.

The curious thing about all this is that I have found no mention of it in any guide-book but an ounce of discovery is more exciting than a ton of directed sightseeing

* * *

Our children's physician arrived unusually late for lunch, and remarkably contented with life. The morning had produced a clinical pearl, some rare syndrome with real honest-to-goodness physical signs that she could demonstrate to the students It had made her day, shedding a glamour over an outpatient clinic normally recruited from the young owners of running noses and capricious appetites We congratulated her and then asked each other to describe what transformed a routine session into a memorable one. What makes your day?

The radiologist admitted to an inordinate, if private, satisfaction when an X-ray revealed a lesion which had been unsuspected or overlooked by the clinicians The pathologist enjoyed drawing blood (and marrow) from metaphorical stones Our neurologist's cup of happiness overflows whenever he is able to establish an exact diagnosis, apparently this happens excessively rarely The surgeon was spoiled for choice All his performances were spectacular—we gathered that was the reason operations were done in theatres But there were subtle joys—deftly setting a transfusion going into some secret, invisible, impalpable, fully-patented-in-all-major-countries venule at the base of the little toe, after the anæsthetist had ploughed up all the official veins The anæsthetist said, somewhat bitterly, that the sight of a surgeon including his own little finger in a ligature, or his screams as he snipped off the tips of his glove in the course of some fancy piece of scissor-work, rendered an operating list more than tolerable

And we know, too, what makes a child psychiatrist's day He told us, when he had worked his way through the 2*s* 8*d.* luncheon, as he left for an unexpected afternoon's golf It is a last-minute cancellation of outpatient appointments en masse.

* * *

During the years we lived in a Cockney Terrace in Lambeth it mystified (and sometimes irritated) me, the way all my colleagues up and down would address me firmly as "Mr" The houses, though elegant Georgian of the most sought-after type, had not contained a professional man for a century or so Consequently Tom the taxi-driver, Ron the docker, Charlie the plumber, and others were a little uncertain about us and it wasn't until our kids were old enough to join in the local destructive activities that the ice (among other things) was broken. Thereafter, baby-sitting was no problem, nor the odd half-loaf on Sunday plus those other little neighbourly services that make urban life possible. In return I catalysed the admission of some ailing relatives to various kinds of hospital and acted as informal P.R.O for those places when things seemed not to be going right. (How badly hospitals need an effective information service) So they knew obviously enough that I was a doctor, but still they called me "Mr"

I never understood why until after I had left the terrace for bourgeois Beckenham. Then on holiday with a cockney couple in a remote farmhouse I was submitted to a further barrage of "Misters", and I overheard Mrs Elephant and Castle telling her children severely "You must not call the doctor 'Dr', because he is on holiday and not doing his work now" So all that time my old pals had merely been honouring my off duty How little people understand each other!

* * *

We were surprised and delighted at being invited to a barbecue at the local mental hospital, for my associations with it are tenuous The feast proved to be a monumental affair, a huge gathering of medical and ancillary staff with their wives or husbands There was a vast array of food spread out on the immaculate lawn, and an apparently limitless supply of wine. During the evening I heard the M.C. of liquid, the deputy medical superintendent, proudly declaring as he hurried back to the reserve depot, "That makes 80 bottles so far"

One of the staff let me into a secret when I commented on the supreme generosity of the hosts "As things are here," he said, "one firm deals with the majority of the aged inpatients and naturally that firm gets most of the cremation certificate fees We decided that the fairest way of dealing with them was to pool them. And this seemed to be a suitable way of disposing of the fund."

A long time later we gave our parting thanks to the medical superintendent, and he replied, "See you next year, all being well?" As we walked away, well satisfied, I felt that the glare of the huge charcoal fire was singularly appropriate.

* * *

News from School—I have ordered a new sports jacket, but it takes about 3 weeks to come from London I really am ashamed of my suits now, as they are very small and *rotting* on me That is not very surprising, is it?

Letters to the Editor

USE OF BRL.1241

SIR,—I read with some dismay in the article by Professor Elek and Dr Fleming (Sept 10) that the authors had sprayed large quantities of the new penicillin derivative, BRL 1241 (' Celbenin '), on to an entire hospital ward in an attempt to eliminate nasal reservoirs of staphylococci

The authors have justified their procedure on the ground that the drug is an " unnatural " compound and that therefore clinically significant resistance to it in the form of an enzyme capable of destroying it is " highly unlikely " Supposed " naturalness " or " unnaturalness " are doubtful criteria for predicting the susceptibility of compounds to attack by microorganisms, as is shown by the wide variety of substances that are readily degraded by common soil bacteria equipped with enzymes that must somehow have previously evolved It is likewise evident that penicillinase itself is the product of a previous evolutionary process Further, it is safe to say that at the present time there is knowledge neither of the specific molecular relationships between penicillin, penicillinase, and the genetic apparatus which determines the enzyme's structure, nor of the evolutionary process(es) whereby novel enzymes arise and existing ones are altered Thus it is difficult to see any justification for the ex-cathedra statement that a mutation resulting in a new or modified penicillinase able to destroy BRL 1241 is " highly unlikely" because the compound is not " natural"

Although in fact staphylococcal penicillinase does not attack the drug and, in the studies published to date, significant resistance has not been encountered in vivo, it is nevertheless true that *Bacillus cereus* penicillinase does hydrolyse BRL 1241 [1] and the finding in this laboratory that *B cereus* is resistant to its antimicrobial action came as no surprise Also, resistant mutants of staphylococcus have been isolated readily in vitro in this laboratory and in the laboratory of Dr Mary Barber,[2] and it is therefore not safe to assume that clinically significant resistance cannot just as well arise in vivo It is at least certain that if such resistance can be developed, the method used by Elek and Fleming is as well adapted as any other to elicit it Moreover, the ubiquity of penicillin is well known to have contributed materially to the replacement of penicillin-sensitive staphylococci by resistant ones, should a BRL 1241-resistant strain appear, large quantities of the drug widely distributed can surely be expected to have the same effect

Admittedly the authors were able to achieve their aim of eradicating nasal staphylococci and in so doing to reduce the incidence of staphylococcal infection on their experimental ward without the development of demonstrable resistance on the part of the organism Thus the objections raised in this letter may be regarded as theoretical, it is conceivable that the method might be used indefinitely without unfortunate consequences, and it could be argued that the risk involved is acceptable in view of the advantages This risk must however be assessed in the light of the history of the fight against the staphylococcus which has been a continual effort to find new drugs with which to keep pace with the emergence of resistant pathogenic strains

We should not lightly disregard this history and its lesson is that the valuable properties of BRL 1241 in treatment of penicillin-resistant staphylococcal infections themselves impose an obligation to cherish and guard it carefully lest history repeat itself once again and we be left with just one more ordinary antimicrobial drug. In accordance with the established principles of antimicrobial therapy, BRL 1241 should be used exclusively for the destruction of penicillin-resistant staphylococci and its primary use should be in the treatment of actual infections Should it be desired to eliminate such organisms from the nasal passages and elsewhere, then the administrative inconvenience entailed by effecting this on an individual basis is surely not too great a price to pay for the avoidance of the risk inherent in wholesale dispersal of the drug

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RICHARD NOVICK

SMOKING BY ADOLESCENTS

SIR,—Earlier this year you published [1] an appraisal of Edinburgh's vigorous and highly organised campaign against cigarette-smoking This was carried out in response to the Government's request in 1957 that all local authorities educate the public about the dangers of cigarette-smoking particularly in its relation to lung cancer The inquiry showed that the campaign had no significant effect in persuading people to give up smoking The only encouraging result was a change in the public attitude towards smoking in young people More thought it wrong, and parents with young children over the age of 15 years were now more inclined to regret that their children smoked

This generation developed the habit in ignorance of the hazards involved because it is less than 10 years since the causal relationship between cigarette-smoking and lung cancer was firmly established It is surely our responsibility to make sure that our children do not fall into the same trap This will not be easy because they are constantly exposed to the most subtle and persuasive propaganda Cigarette-smoking is becoming increasingly common in television programmes where it is particularly dangerous because of the high regard in which the participants are usually held We know the habit to be already widespread in secondary schools, and in junior schools it is not unknown

With the present generation firmly in their grip cigarette manufacturers are making every effort to gather our youngsters into their net Last year they spent £5,000,000 on advertising—more than half of this on television In 1953, before the days of commercial television, it was £1,000,000 The first quarter of this year showed a startling advance of 60% in advertising expenditure over the first quarter of 1959 It is perhaps not without significance that the post-war bulge babies will be reaching the age of persuasion in 1962–63, and surveys have shown that once a person reaches the age of 18 without becoming an habitual smoker it is unlikely that he will become one The tobacco manufacturers are concentrating their promotional efforts on teenagers and other young smokers who are not yet set in their ways In the words of one of their advertisers, they " looked for an idiom in which they could talk to the young people in their own language " and this is very obvious in their more recent advertising approach which shows how life can be more wonderfully enjoyed trailing clouds of tobacco smoke in Elysian surroundings

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[1] Stewart, G T *Brit med J* 1960, ii, 690

[2] Barber, M *ibid* p 939

[1] *Lancet*, 1960, i, 327

Edinburgh has shown that even the most efficient municipal endeavour is not enough It is obvious that a high-level national effort is required to deal with a habit to which resistance is so difficult to overcome Only a few people die from poliomyelitis or diphtheria, yet it is rightly considered necessary to carry out a national immunisation campaign Many die from accidents on the roads, and through television programmes and other media the importance of road safety is constantly impressed upon us Lung cancer annually kills four times as many people as are killed on the roads but no equivalent effort is made to fight it Although the advertising of remedies purporting to cure certain diseases is forbidden by law the Press and television are permitted to advertise tobacco products which can cause avoidable and often fatal disease It seems reasonable to ask that using the same powerful media action be taken to show the public, and particularly our young people, the other side of the picture

Dealing with this issue in its recently published report the Joint Tuberculosis Council states that " we are faced with a health problem of great magnitude and not enough has been done centrally to safeguard the public welfare " It goes on to ask, " is it really in the public interest to allow unrestricted advertisement of a substance which reliable evidence suggests is dangerous to health? Are the preventive steps already taken commensurate with the gravity of the situation?" In the opinion of the Council they are not

We who each year are being called upon to treat an ever-increasing number of cases of lung cancer, coronary thrombosis, and chronic bronchitis must share the opinion of the Joint Tuberculosis Council that this growing threat to the public's health should be approached with a greater urgency than is at present apparent

Edinburgh S LIPETZ

SIR,—May I support Dr Learoyd's letter of Oct 15?

Having worked in hospitals for nearly 30 years, and having been a 20-a-day smoker until June 30, 1954, I agree entirely that it is the adults who stand indicted of mass murder by example. I also agree that action would have been taken about the 20,000 lung-cancer deaths, but for the vested interests—but, Dr Learoyd, may I as a layman make an appeal to your profession to set a special example

My many medical colleagues smoke, I believe, more than the average adult male. At a national conference I asked a former Minister of Health if he would advise hospital management committees to discourage smoking in hospitals, he replied that it was not for the central authority to lay down regulations, that it was up to the local committees to decide this problem at their level

During a recent visit to America, I was impressed by the effort being made in some hospitals to make the hospitals the centre of community health These hospitals had health museums and encouraged the local people, especially young people, to visit the hospital to learn how to care for their bodies

If ours is a Health Service, let us stop working a Sickness Service, and let us encourage our young people to live healthily, which among other things means *No Smoking*

Edinburgh T W HURST

ARTIFICIAL INSEMINATION

SIR,—This correspondence began as a result of a reference to theological tenets in a leading article The whole point of my first letter was to point out that the moral theology on A.I.D cannot, from the nature of things, undergo change or " move with the times " Dr Jackson, with all due respect, has lifted the argument out of its theological context My original letter was not concerned with any definitions other than the theological one It is possible to say with Humpty Dumpty " A word means just what I choose it to mean ", but this cannot alter the definitions given within the confines of moral theology

Hale, Cheshire AUDREY F ROBERTS

ENZYME DEFICIENCY IN HÆMOLYTIC DISEASE OF THE NEWBORN

SIR,—The very interesting article of Oct 15 by Captain Weatherall describes red-cell enzyme deficiency in infants in Malaya with hæmolytic disease in the neonatal period He relates this finding to the type of enzyme deficiency found in certain patients with toxic hæmolytic anæmias due to drugs [1]

The occurrence of such a hæmolytic condition is of great interest, but I am by no means sure that the findings should be interpreted as indicative of spontaneous intravascular hæmolysis in a group of primaquine-sensitive infants Evidence that the cells of such individuals will undergo spontaneous hæmolysis in vivo is at present scanty, and in the absence of a history of drug administration or the ingestion of chemical poisons such spontaneous destruction would be surprising

The principal metabolic abnormality demonstrated in these cases—deficiency of glucose-6-phosphate dehydrogenase (G-6-P D)—has been shown to be present in another disorder, congenital non-spherocytic hæmolytic anæmia [2,3] In this condition, a severe neonatal jaundice or anæmia is a well-recognised presenting feature,[4] and such children have been previously misdiagnosed as cases of erythroblastosis fœtalis [5] The other findings reported by Captain Weatherall would be compatible with a diagnosis of congenital non-spherocytic hæmolytic anæmia, and in 1 of the 3 surviving patients a low-grade hæmolytic process was thought to be continuing four years later

Certain features in the laboratory findings serve to differentiate the congenital non-spherocytic group from those belonging to the primaquine-sensitive variety Selwyn and Dacie [6] described tests based on observation of the effect of added glucose on fragility and autohæmolysis estimations, while Zinkham and Lenhard [3] have shown that the presence of a reticulocytosis does not, in the congenital non-spherocytic group, result in an increase in G-6-P D activity as is found in the case of primaquine reactors The red-cell metabolic defect appears to be more severe in the congenital non-spherocytic group, and spontaneous destruction of the cells in vivo is a characteristic finding

A further large group of cases of neonatal jaundice in children in Malaya was reported by Smith and Vella [7] They found G-6-P D deficiency in 19 out of 20 cases investigated This series is not so fully reported as the cases described by Captain Weatherall, and it is not clear whether all were suffering from actual hæmolysis or merely neonatal hyperbilirubinæmia of hepatic origin It is clear, however, that a syndrome of this type is common in Malaya If the supposition that these children suffer from congenital non-spherocytic hæmolytic anæmia should be correct, it seems possible that this inheritable disorder is commoner in Malaya than in other parts of the world

Congenital non-spherocytic hæmolytic anæmia is still regarded as a rare condition, and family studies using the most recent biochemical techniques are infrequent This combined group of patients in Malaya may represent the largest number of cases available for study so far The results of further investigations, particularly the application of tests which will distinguish the congenital non-spherocytic group from other hereditary metabolic abnormalities of the red cells, would be of the greatest interest

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[1] Beutler, E., Dern, R. F , Flanagan, C L., Alving, A S *J Lab clin Med* 1955 45 286
[2] Newton, W A., Bass, J C *Amer J Dis Child* 1958, 96 501
[3] Zinkham, W H , Lenhard R. E. *J Pediat* 1959, 55, 319
[4] Dacie, J V The Hæmolytic Anæmias London, 1960
[5] Bruton, O C., Crosby, W H., Motulsky, A. G *Pediatrics*, 1954, 13, 41
[6] Selwyn, J G , Dacie, J V *Blood*, 1954, 9 414
[7] Smith, G D , Vella, F *Lancet*, 1960, i, 1133

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C S PITCHER

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Surely what distinguishes the pathology of coronary thrombosis in the younger and older age-groups is not the nature but the distribution of the lesions

Yater et al [1] showed that in the younger group pathological changes were confined to the heart itself In the older group, where the condition was part of a generalised atherosclerosis, they were of course more generalised

This is what makes "young or middle-aged man's" thrombosis a separate and more interesting disease Presumably, but this has not been written up, many of these cases are not associated with hypertension This difference may also account for the differential death-rate between men and women under 64 Women (and apparently Seventh Day Adventists [2]) do not get coronary thrombosis as a localised disease

Possible factors to produce coronary thrombosis in the executive-administrative class have been reviewed recently [3]

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H BERIC WRIGHT

KIDNEY HOMOTRANSPLANTS

SIR,—In your issue of Sept 10 I read with interest of yet another successful renal homograft in twins and your leading article on kidney homotransplants in man While you pay due respect to the advances made in our understanding of homograft acceptance and rejection, work issuing notably from your country, it occurs to me that most papers on tissue transplantation in man fail to consider one important aspect of this problem

We have learned from the work of Owen, Medawar, Billingham, and others that a lifelong tolerance is conferred upon the heterosexual bovine pairs possessing placental vascular communications which also result in the sterilisation of the female twin—the freemartin A fact not usually appreciated is that the majority of human single-ovum twins has just such anastomoses in the placenta In man approximately 80% of "identical twins" have a monochorial placenta Over 90% of these can be shown to have vascular communications of one kind or another between the two fœtal circulations Indeed, the flow in these channels occasionally is unidirectional

Is it not conceivable that transplantation success in human twins could be the result of such anastomoses, as is the case in cattle? In most cases of human tissue transplantation the placental condition is unknown At this time our knowledge is inadequate to predict whether monovular but dichorial twins would exchange grafts freely It is not evident from the published reports of successful transplants in twins that it is the genetic constitution of the twins which is the basis for acceptance It could be an acquired type of tolerance

The case of Merrill and his colleagues [4] cannot be regarded as necessarily proving dizygous (fraternal) twinning on the basis of unilateral graft rejection, especially not in the light o what they choose to call "consanguinity" in 25 blood-groups Other authors use such concordance as main arguments i favour of identity In fact, it is difficult and often impossibl to establish proof for monovular origin in dichorial twins Merrill et al [1] were cautious to label the twins as non-identical rather than fraternal It is well known that non-identical monovular twins occur frequently. Since their dissimilarity can extend to severe unilateral malformations one can reason that it could also, on occasion, involve histocompatibility genes

The point I wish to make is that obstetricians should begin to document carefully the placental conditions in twins for the benefit of the twins and science

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KURT BENIRSCHKE

TREATMENT OF URTICARIA

SIR,—Having heard something of Dr Sidi's results (Oct 15) in the treatment of urticaria with antimalarials, and prompted by the experience of Sir Charles Dodds (Oct 22), I have recently carried out a clinical trial of proguanil ('Paludrine') in the treatment of chronic urticaria This was carried out at St John's Hospital for Diseases of the Skin, where my colleagues kindly sent cases to me for study

18 patients have taken part in the trial, of whom 9 were men and 9 women Ages ranged from 20 to 72 years Duration of urticaria ranged from four weeks to three years

Of these patients 9 were given one period of treatment and after an interval later re-entered the trial, so that altogether 27 observations have been made

Capsules were prepared containing 100 mg of proguanil or 100 mg of sodium bicarbonate Each patient was given 28 capsules of one or other kind with instructions to take one capsule twice daily for a fortnight Proguanil or sodium bicarbonate was serially allotted to patients according to a previously prepared random order When patients re-entered the trial a second time they were treated as new patients, and therefore received either the same or a different treatment from the one they had had the first time Neither the patient nor the doctor knew which treatment was being given until the conclusion of the entire series

The results were as follows

	Cleared	*Improved*	*Total Improved*	*Doubtful*	*Failed*
Proguanil	3	2	5	3	5
Bicarbonate	0	2	2	1	9

Cleared means that all urticaria had ceased by the time the patient was seen at the end of a fortnight's treatment

Improved means that the patient stated that the urticaria was less than before treatment and less than had previously been experienced as a spontaneous fluctuation

Doubtful means that improvement observed, if any, was within the range of previous spontaneous fluctuation

Failed means that during the fortnight's treatment the eruption remained unchanged or became worse

2 patients failed to re-attend for treatment, leaving 25 who were available for assessment

Of the 3 patients who cleared with proguanil, 1 had previously shown improvement on bicarbonate Of the 2 patients who improved on proguanil, 1 later re-entered the trial and failed on proguanil, the other later re-entered the trial and made a similar improvement on bicarbonate

The assessment of the value of treatment in chronic urticaria is difficult for three reasons first, because the disorder itself fluctuates in severity in an unpredictable way and eventually clears up or remits independently of treatment, second, because at the time of examination the eruption is often not present and the estimation of its severity has to be made entirely by the patient, third, because chronic urticaria is much subject to psychological influences and the results of treatment are likely to be considerably influenced by suggestion Because of this I believe that only a blind controlled trial is likely to give reliable information

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[1] Yater, W M, Traum, A H, Brown, W G, Fitzgerald, R P, Geisler, M A, Wilcox, B B *Amer Heart J* 1948, 36, 334
[2] Wynder, E L, Lemon, F R, Bross, I J *Cancer*, 1959, 12, 1016
[3] Wright, H B *Practitioner*, 1960, 184, 765
[4] Merrill, J P, Murray, J E, Harrison, J H, Friedman, E A, Dealy, J B, Dammin, G *New Engl J Med* 1960, 262, 1251

The trial which I have briefly mentioned had negative results, but one cannot of course prove that proguanil was ineffective One can only say that in these 25 tests no convincing evidence of effectiveness emerged I appreciate, of course, that proguanil is not the same as amodiaquine, which Dr Sidi and Dr Reinberg used, it was chosen in my series because of its freedom from side-effects

These results do not necessarily indicate that the antimalarials are never effective in chronic urticaria One may well suppose that the symptom is the end-result of a variety of different causes or mechanisms and that an antimalarial may break a link in pathogenesis in one case and not in another This may explain the occasional remarkable case where the effectiveness of an antimalarial seems to be undeniable although it cannot be regularly obtained in other patients

London, W 1 F RAY BETTLEY

COMMUNITY MENTAL CARE ?

SIR,—Psychiatry is following good precedents as it evolves and develops a social conscience It is turning from a preoccupation with those human abstractions of natural processes that are labelled " diseases " to prevention and to the promotion of mental health

Mental health is, however, too vast and too important to be delegated to any one section of medicine Fortunately, the barriers that isolated psychiatry from the main currents of medicine (a subject discussed in your leader of Oct 15) are being eroded from both sides Your report that general practitioners and medical officers of health recently conferred with psychiatrists on mental health is a welcome illustration Others among us are also concerned, and pædiatricians especially so, if only because so many mental disorders have their roots in the early years of life

But mental health is too vast and too important to be delegated exclusively even to the medical profession Allies are needed outside medicine and its traditional associates (such as psychologists and social workers) Geneticists, biochemists, sociologists, and anthropologists surely have fundamental contributions to make So also have those non-medical agencies concerned with moral welfare, with family life and with education—of parents and of children An enterprising pilot scheme inaugurated by Dr S Lebovici in a whole sector of Paris has already shown that school teachers, for example, can play a very important part in the prevention and early case-finding of mental disorders

" Is the community ready for prevention ?" was asked at a recent conference on preventive psychiatry [1] While that question is being pondered some of its implications will also be weighed To prevent assumes that we know what is undesirable To some extent we do know, but we need to know much more In *The Common Sense of Science*, J Bronowski quotes William Clifford, geometer and philospher, who wrote of scientific thought " The truth at which it arrives is not that which we can ideally contemplate without error, but that which we may act on without fear " I believe that in the field of mental health, psychiatry and medicine should augment their forces in order to establish a substantial basis on which to act without fear

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Bristol JOHN APLEY

CONSERVATION OF THE OVARIES

SIR,—Your annotation of Oct 22 on conservation of the ovaries at hysterectomy is timely The removal of *normal* ovaries before the menopause as prophylaxis against subsequent carcinoma is physiologically and psychologically indefensible Even if the ovaries are cystic an attempt should be made to conserve ovarian tissue In the rare event of the pathological examination revealing malignancy then I admit a further laparotomy would be necessary But I believe this course is preferable to the wholesale sacrifice of ovaries, normal and cystic, that is such a common practice

If we accept Jeffcoate's [1] estimate that only 1 case of ovarian cancer can be prevented at the expense of 5000 hysterectomies and Schabort's [2] recent figure of 2 in 5000, then there is no place for routine oophorectomy Osteoporosis and atherosclerosis are now recognised as complications of the normal and artificial menopause but the profound psychological disturbances that follow the latter have received insufficient emphasis It is the family doctor who has to deal with these and not the surgeon since the patient never wants to see him (or her) again

A woman has an emotional attachment to her uterus and ovaries and it is unfortunate that her gonads, unlike the testicles, are not in an extracorporeal pouch secure from unnecessary extirpation

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THE RESERVED £1 MILLION

SIR,—As members of the General Practice Reform Association, we note with approval the aim of the joint working party to raise standards of general practice, and to investigate methods of distribution of remuneration which will help to achieve this end

We believe that the most effective way of improving the quality of practice is to give every possible encouragement to the practitioner to keep up to date and to extend his knowledge of medicine, and to cooperate more closely with his colleagues in the hospital service

Accordingly, we should like to suggest that the £1 million be used to finance the setting up of paid clinical assistantships for N H S general practitioners in general hospitals We suggest that such clinical assistantships should be made available, in rotation, to all general practitioners who desire them, and in as many clinical specialties as possible Clinical contact between consultant and general practitioners would prove stimulating to both parties, and the hospitals would benefit in the long run through having fewer patients referred for consultant opinion

At present, general practitioners who work part-time in hospitals are remunerated from hospital sources We can see no insuperable practical objections, however, to altering this system so as to pay for clinical assistantships out of the central pool, and we feel that the benefits of our proposal would outweigh any minor administrative difficulties At the rate of remuneration recommended by the Royal Commission for general practitioners working in hospitals (£215 p a per notional half-day) the £1 million would enable every principal in the N H S to serve as clinical assistant, in one or more specialties, for one half-day per week for six months in every thirty months All G P s would be enabled to share in the money, and controversial proposals for " merit awards " for particular practitioners, or for payment for specified items of service (involving more paper work in making claims) would be obviated

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[1] *Times Educational Supplement*, Sept. 30 p 387,

[1] Jeffcoate, T N A Principles of Gynæcology, p 667, London 1957

[2] Schabort, J W *Trans Coll Physns Surg Gynæc S Afr* 1960, 4 11

A C McLeish
Chairman

A C J Saudek
Secretary

General Practice Reform Association,
London, N W 6

TRUE HERMAPHRODITISM AND KLINEFELTER'S SYNDROME

Sir,—Perhaps if we had entitled our report of Oct 1 "Chromosome count in a hermaphrodite who *presented* with some of the features of Kleinefelter's syndrome" we would have described better what occurred and would have avoided some of the criticism of Dr Bishop and Professor Polani (Oct 23) We still maintain, however, that when a male person presents with eunuchoid proportions, female pubic hair, absent facial hair, gynæcomastia, and a small testis (how small must it be?) then the possibility of Kleinefelter's syndrome must be considered in view of its reported relative frequency If he turns out to be "chromatin-positive" then we feel that all these facts constitute "some features" of the syndrome whatever the eventual diagnosis may turn out to be We believe also that the pathology of the testis was quite compatible with the diagnosis, especially since there was no evidence at the time of overstimulation of the testis by the pituitary

There is no doubt now that we should initially have been more alert to the possibility of hermaphroditism, and it was in an effort to warn others who might be placed in a similar position to ourselves that we included any reference to Klinefelter's syndrome at all By changing the time factor only slightly we could easily have reported the chromosome analysis in a hermaphrodite whom, in retrospect, we had diagnosed clinically with the same assurance as Dr Bishop and Professor Polani

R R Gordon
F J P O'Gorman
C J Dewhurst
C E Blank

City General Hospital,
Sheffield

PERPHENAZINE IN HUNTINGTON'S CHOREA

Sir,—Dr Pakenham-Walsh (Oct 1) is to be congratulated on what may be an important therapeutic observation No doubt in his desire to be brief one or two points remain obscure and on these we would welcome enlightenment

(1) The grounds on which he makes the diagnosis of the "hereditary chorea" of Huntington

(2) Why he does not include in his therapeutic target the numerous choreo-athetoses accompanied by progressive intellectual deterioration arising from other causes

(3) Why he does not include cases of choreo-athetosis not associated with dementia

Stella Conway
R H Boardman

Herrison Hospital,
Dorchester

⁂ We showed this letter to Dr Pakenham-Walsh whose reply follows —Ed L

Sir,—The diagnosis was made essentially on clinical grounds Both patients exhibited characteristic mental and physical symptoms and signs I agree that in case 1, as far as we were able to determine, we could obtain no unequivocal evidence of a positive family history, and in case 2, this could not be obtained because he was a Ukrainian displaced person and no history whatsoever was available from his family background In spite of these omissions, however, the cases were so typical that there was little hesitation in diagnosing them as Huntington's chorea

As far as other choreo-athetotic conditions are concerned, we will certainly attempt a diagnostic evaluation and treatment in the light of our present therapy This therapy appeared to me to be so significant, however, and it seemed of some interest and importance in such an intractable state, that publication was justified if only to draw attention to the potentialities of the drug and if possible to confirm this with other centres

Lancaster Moor Hospital,
Lancaster

R Pakenham-Walsh

SPORTS MEDICINE

Sir,—I do not agree with Dr Troup's statement, in his interesting article of Sept 24, that "medicine is not very clever when it comes to coping with the sprains and strains to which athletes are subject" It would be more true to say that the knowledge of how to treat these disabilities has been known and practised with good results, for many years, by a very small minority of the profession Several excellent writings on the subject have been made in the past by many authors—e g, Sir Robert Jones, Sir Morton Smart, Bristow, Mennell, Tucker, and latterly Cyriax, as mentioned in Dr Barbour's letter of Oct 8, but little interest has been shown by the profession in learning from their works

Until three years ago I was in the R A M C, where I had considerable experience in the treatment of athletic injuries, treating them along orthodox lines, and I thought that I knew a great deal about their management Now, however, I realise that the methods I used did not produce the quick results which can be obtained by following a few simple rules Athletic injuries are a specialised field, and yet good results can be obtained by anyone sufficiently interested to learn these few basic rules, most of which are frequently broken even by prominent orthopædic surgeons

These rules are

(1) An exact diagnosis must be made If complete rupture of a ligament or tendon is diagnosed, then immediate operative repair must be performed

(2) Prompt reduction and elimination of traumatic swelling This is accomplished by aspiration of hæmatomas, or incision and evacuation of clotted hæmatomas, injections of hyaluronidase to assist the spread and absorption of traumatic swelling and effusion, the use of pressure bandages, physical treatment consisting of massage with the limb in elevation and faradism to the affected muscles

(3) Rest and support the damaged structures by means of an easily removable splint, so that home treatment consisting of remedial exercises in relation to contrast baths and self-massage can be performed up to four times a day, and also so that physical therapy can be given

(4) Remedial exercises are given Isometric exercises which are performed with the splint on, to maintain the power of the muscles, and isotonic exercises with the splint removed to coax and increase the range of movement of the joints affected and prevent the formation of adhesions These must be very carefully supervised, a correct balance between rest and activity being obtained the dictum is "rest from strain, but exercise without strain"

(5) Correcting postural faults and teaching the patient "active alerted posture"[1] This ensures that each joint at all times is under muscular control so that strain is removed from the affected joint, the injured structures thus recovering more quickly This also assists materially in preventing recurrences

(6) During the recovery period it is essential to make sure that muscles which have been damaged, or muscles acting on a

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[1] Tucker, W E (1960) Active Alerted Posture London

joint which has been injured, regain their full length in relaxation as well as their full power of contraction Otherwise when violent activity is resumed muscle tears or symptoms of joint strain will recur This full relaxation is obtained by massage, by gentle stretching of the muscles, and by manipulations of the joints during the healing process to prevent contractions Attention must be paid to the range of movement of the joints above and below the affected joint to ensure this

(7) Occasionally in spite of this treatment full functional recovery is obtained only by manipulation of a joint or stretching of a muscle under general anæsthesia.

London, W 1

R P GOULDEN

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—At this hospital I think we have found the answer to the problem of administration in mental hospitals, although, of course, this solution, like any other, has its defects

We have divided the hospital into three independent clinical teams of 300 beds each Each team has its own admission wards and long-stay wards and each team has its own outpatient clinic The teams consist of a consultant in charge, S.H M.O , and two junior doctors, one being a registrar and the other a J.H M O The third team has two consultants who share responsibility on an equal basis, each consultant having his own share of the admission beds The consultants have absolute clinical control of their teams It is firmly accepted that the consultant is fully responsible for the patients under his care and that the medical superintendent has no right to interfere in his clinical *freedom* Each *consultant, therefore,* is responsible for his own correspondence, which does not go through the medical superintendent's office

Each consultant and S H M O are " on take " for a week at a time, and unless a general practitioner asks for a particular consultant the one " on take " is responsible for all domiciliary visits and emergency visits to other hospitals in the area All acute admissions go on to the ward of the firm " on take " for the week.

The medical superintendent has his own firm, which he shares on an equal basis with the consultant who is also in charge of the E E G department

Each firm has its own social worker, assistant matrons, chief male nurse, and mental welfare officers At the present time the distribution and administration of the nurses is still essentially controlled from the nursing office of the respective sides of the hospital, but we rather hope that eventually each firm will be responsible entirely for its own nursing organisation

The medical superintendent is the coordinator of the teams in the sense that he is chairman of the weekly senior staff conference. He is the liaison officer between medical staff and management committee He attempts to act as a mediator and moderator between medical and nursing staff on the one hand and administrators on the other (areas of traditional misunderstanding and friction) As far as the hospital management committee is concerned he is answerable to them for the efficiency of the medical work of the hospital Although there is something to be said for doing away altogether with a " board-appointed " superintendent and adopting the general-hospital pattern of medical staff committees, the following points should be borne in mind

(1) However good the lay administrator may be, in the last analysis it must be the medical staff who should approve or disapprove of such things as plans for new wards, their furnishing, and various other domestic matters which do in fact have a great effect on the patients lives, especially in a mental hospital This work of liaison can perhaps better be done by a man who is permanently appointed to the office, because he has powers of decision and authority not available to an elected chairman of a medical staff committee Therefore, if the medical side are to have this effective say, it can be better done through one doctor who, being permanent, the administration get used to, who has the right to attend all H.M.C meetings, and who is officially recognised as responsible for medical organisation, because then the H.M C have to take more notice of his monthly reports than the resolutions of medical advisory committees In addition he is able to take decisions on the spot rather than having to refer matters back to committees which may only meet once a month

(2) Mental hospitals are only dealing with one type of patient, and therefore it is much easier for one doctor to act as director than in a general hospital in which there are many different types of patient During the next ten years we shall probably see mental hospitals with and without superintendents, and it will be possible then to judge the merits of the two systems One thing, however, is certain that the old autocratic administrative superintendent is a person of the past The modern superintendent, director, or coordinator must be first a clinician with his own team, and his administrative duties are those of coordinator, catalyst for new ideas, moderator and authoritative voice of the medical staff, although like any chairman he is free to express his own independent opinions apart from those of his colleagues but not instead of them as used to happen in the past

Towers Hospital,
Humberstone,
Leicester

H B KIDD

PERITONEAL SPLASH A PHYSICAL SIGN

SIR,—The letters by Mr Lane Roberts (Sept 24) and Mr Smiddy (Oct. 15) on the signs of perforated ulcer are very interesting Like Mr Smiddy, I have found that this sign can be somewhat unreliable, and that even under anæsthesia both false positives and false negatives are obtainable

May I draw attention to another physical sign in perforated ulcer which seems to receive little attention ? If a patient who is suspected of a perforated ulcer is raised actively or passively into a sitting position, he often complains that the pain is produced high in the interscapular region This is often present when many other signs are absent, and is useful in the longstanding perforation, where the only appearances are of general peritonitis, but where a history of sudden onset of pain raises the possibility of a perforated peptic ulcer It is not present in my experience with perforations of other viscera

The General Hospital,
Birmingham

GEORGE T WATTS

SCHOOL DENTAL SERVICE

SIR,—The future of the school dental service, which was dealt with in your annotation of Oct 15, was also discussed in last week's *Local Government Chronicle* Both journals suggested that the school dental service should be completely reshaped This seems to be a drastic step to take when a few adjustments in the present administration should solve most of the problems which exist at present There seems to be no need to set up a separate department, as the administrative services at present available in the health department can cope with the work of the school dental service Provided the principal dental officer is given proper status he will be no more controlled by the medical officer of health than is the ophthalmologist who works for the health department on a sessional basis

The only changes that appear to be necessary are firstly that the salary scale of a dental officer should be an approximate assimilation of the assistant medical officer and senior medical officer scale That is £1300–£2200 Where there is an establishment of four or more dental officers there should be a principal dental officer, who should be paid the same salary as a principal medical officer An officer entering the service should receive one increment for every year he has spent in military or civilian practice

These changes in the salary scale, along with inducements such as a car allowance, five-day week, and paid evening sessions, which the more enlightened authorities already provide, would make the service more attractive and would probably encourage some of the dentists in the older age-group to transfer to the service when they felt they could no longer keep up the pace required in private practice.

MEDICAL ADMINISTRATOR

ASSESSMENT OF HEPATIC SIZE, SHAPE, AND CONTENT

SIR,—Your annotation of Oct. 1 does not mention a valuable method for determining the liver size. By peritoneoscopy a suspected hepatomegaly can easily be confirmed and the relations of a palpable abdominal mass to the liver and gallbladder verified. (Without laparotomy the diagnosis of a Riedel's lobe and a polycystic liver can be made only by peritoneoscopy.) The method is of great value for identifying hepatic metastases before operation, and only tumours deep in the hepatic parenchyma cannot be seen. Explorative laparotomy, as suggested by Mr. Grimshaw (Oct. 8), may thus be replaced in most cases by peritoneoscopy, which, when not combined with biopsies, &c., is almost completely safe and is well tolerated by the patients.

Rigshospitalet,
Copenhagen.

K. WINKLER.

THE BORDERLINE FOR SEVERE SUBNORMALITY

SIR,—With the start of the Mental Health Act (1959) on Nov. 1, the problem of the borderline between conditions of incomplete mental development becomes an important practical consideration.

In mental-deficiency practice in the past, it has been customary to differentiate degrees of incomplete development of mind in terms of, on the one hand, the "low-grade" (idiots and imbeciles), and on the other, the "high-grade" (feeble-minded), with an I.Q. of about 50 commonly acknowledged as the dividing-line. Below this level, pathological ætiology predominates and the prognosis for an independent life is exceedingly poor, and above it, subcultural ætiology and a relatively good prognosis are common. This, too, accords well with the observation that above I.Q. 50 or 55 intelligence seems to be distributed in a Gaussian fashion, hence the "high-grade" defective is essentially a "low-grade" normal, whereas the low-grade defective personifies abnormality.

The Royal Commission on the Law relating to Mental Illness and Mental Deficiency (1954–57) suggested application of the term "severe subnormality" to those whose "general personality is so severely sub-normal that the patient is incapable of living an independent life. This group includes all patients at present classified as idiots and imbeciles and *some* (our italics) of those now classified as feebleminded" (Report of the Royal Commission, para. 17). Later, in the same report (para. 193), an intelligence quotient below 50–60 is quoted as "a pointer strongly indicative of a personality so seriously subnormal as to make the patient incapable of living an independent life." Life is of course rarely, if ever, absolutely independent in modern society. Nevertheless, some amenable but at the same time relatively incompetent patients can be trained to earn their living and become tolerably independent in the community, despite their I.Q.s being in the 50–60 range, whereas others, less amenable to advice and help, fail to do so despite having I.Q.s in the 60–90 range.

In the Mental Health Act itself, which of course arose from the Royal Commission's report, severe subnormality is defined as "a state of arrested or incomplete development of mind which includes subnormality of intelligence and is of such a nature or degree that the patient is incapable of living an independent life or of guarding himself against serious exploitation or will be so incapable when of an age to do so." "Nature or degree" are the operative words, and their interpretation is the problem.

In January, 1960, the Ministry of Health (Estab. 3039/25) commented on the new terminology and stated that "severe subnormality" will apply to "a large proportion of patients now classified as idiots or imbeciles *and perhaps rather more than half of the feebleminded*" (our italics). Later still, a Ministry memorandum on parts I, IV–VII, and IX of the Mental Health Act refers to the subnormal as "intellectually dull but their main trouble is often emotional instability." Assuming, as we must, that the term "intellectually dull" is used deliberately and, in conformity with general usage, relates to I.Q.s between 70 and 85, it may be inferred that most patients with I.Q.s below 70 are now expected to be included in the severely subnormal class. Thus the dividing line set somewhere in the 50–60 range by the Royal Commission seems to be moving to 70 or perhaps even to 75, and most patients under care with I.Q.s below 70 stand in peril of being classed as severely subnormal, with the attendant implication (manifestly untrue for many of them) that they may be incapable of leading an independent life when of age to do so. This hospital, for example, has for many years trained such persons for industrial work and normal jobs at normal wages, so that after two years or so in the community they have been discharged from care to an independent life. Official guidance thus appears to be at variance with the spirit of the Royal Commission's report, the Mental Health Act itself and the experience of hospitals with progressive policies of training or treatment, not to mention the recommendations of the World Health Organisation. Moreover, the extended category of the severely subnormal would contain patients with conditions of greatly diverse ætiology, with present assets as disparate as those of the "man-in-the-street" and Albert Einstein, and with vastly different prognoses.

In principle, therefore, it would seem to be more in accordance with the intentions of the Royal Commission that the definition of severe subnormality (which has much in common with that of imbecility in the 1927 amending Act) should continue to apply to those in the now obsolete categories of idiot and imbecile, and those "higher-grade" patients with I.Q.s between 50 and 55 or even up to 60 whose prognosis seems poor because of personality defect. Many witnesses heard by the Royal Commission drew attention to the harm done by mixing patients of differing grades, but at least it was recognised legally at that time that there *were* different grades of patient within the 0–70 I.Q. range. If severe subnormality is to be given a widely extended interpretation, the recognition of differences in both present status and prognosis will tend to disappear, and many of the dangers, of which the Royal Commission, and interested members of the general public were well aware, will tend to recur. Blanket categories are apt to lead to stereotypes and then to blanket forms of treatment—or lack of it.

It must be admitted that our suggestions, which were in fact originally advanced by the Royal Commission, would lead to administrative difficulties in application of the Mental Health Act where older patients under care are concerned. Owing to lack of adequate training facilities in the past, to national unemployment, and to the effects of long-term residence in institutions, many of these though only of subnormal intelligence are too incompetent socially to take an independent place in society. But these are essentially administrative problems, and it would be disastrous to sacrifice hard-won principle to short-term advantage.

The Manor Hospital,
Epsom, Surrey.

J. F. MACMAHON
A. D. B. CLARKE.

MODERN CLINICAL BIOCHEMISTRY

SIR,—There are many occasions when inspired comments about clinical biochemistry are best ignored. Thus it came about that the nonsense written in the Widdicombe File[1] was allowed to pass without comment. But Professor Cappell cannot be allowed to get off scot-free with his article of Oct. 15 entitled Pathologists at the Crossroads. Since it is on only rare occasions that the subject of clinical biochemistry (as a subject) receives any attention in the medical press of this country, perhaps you would allow a professional biochemist to reply at some length to Professor Cappell and to the many others like him.

Professor Cappell regards biochemistry (syn. chemical pathology) as one of the "four branches of pathology." This is not so, for in the hospital where we both work my department of biochemistry is most certainly not a branch of his department of pathology, nor is the biochemistry which I practise a branch of the pathology which he practises. Biochemistry is a science and is defined as the application of chemistry (repeat, *chemistry*) to biology—in the case in question, to that branch of biology which deals with human disease. All biochemistry, without exception, is applied chemistry, and however unpalatable this may be to those who are not scientists, there is nothing that can be done about it. Biochemistry is not, and never was, a branch of pathology.

Much of the routine work in a modern hospital biochemistry department is necessarily carried out by technicians (exactly as in pathology departments), but these biochemical technicians are highly skilled analysts working alongside qualified scientists to whom they can turn for professional advice and assistance. It is deeply regrettable that Professor Cappell should describe these highly qualified scientists as "other workers not medically qualified." It is this deplorable attitude, in very words such as these, which makes it all but impossible to recruit young science graduates into hospital biochemistry departments.

Automation cannot be dismissed in the few words employed by Professor Cappell. There are many snags to it. All clinicians are familiar with the difficult case of acute metabolic upset where 6 to 8 separate chemical analyses must be carried out in the minimum of time in order to help save life. This is the most important part of hospital biochemistry, and in such cases automation is worse than useless. The modern biochemist uses every effort to wean the clinician away from "large numbers of simple repetitive tests" (few of which are as "simple" as they seem), and the bad old days of doing blood-ureas up one side of the ward and blood-sugars down the other, have almost entirely disappeared. In place of this, the clinician has an ever-increasing choice of better and more specific methods of investigating metabolic disturbance. Yet, we must confess that the blood-sugar/blood-urea mentality still persists in certain quarters.

Professor Cappell states that much of the routine biochemistry can be carried out by "workers who are capable of following given instructions." There is no surer way of landing in trouble. It is the most fundamental of all axioms in science that the worker (whether a junior technician or a qualified graduate) must *understand* what he is about to do, before he begins to do it. Not even the most experienced scientist dare ignore this axiom.

The idea that the medical graduate can aspire to a reasonable knowledge of biochemistry by "a year of fundamental study in chemistry" is laughable. Does he start with the Law of Constant Proportions and finish up with heterocyclics—perhaps with a basinful of thermodynamics thrown in somewhere? The major curse of modern clinical biochemistry is that so many people think it a simple little subject that can be mastered in a few months' study. The vision of the young pathologist with "a certain foundation in each of our four disciplines" clearly demonstrates how far the writer is out of touch with modern science. No doubt he would be delighted to have all these four separate subjects grouped together as "pathology" for the greater glory of his own subject. But in the case of biochemistry, which demands so much specialised knowledge of pure chemistry, a "certain foundation" is just not good enough in these days. The hospital of today demands, and is entitled to get, something a good deal better than one-quarter of a jack-of-all-trades who can turn his hand to any odd job. In this modern scientific world, the part-time amateur is definitely out. Pathologists cannot put the clock back half a century.

Admittedly, it is a tragedy that there are large areas where "Clinical Pathology" still flourishes—even in 1960 A.D. There is not much that we biochemists can do about it, we are seldom consulted; the powers that be invariably go to the pathologist for advice. These areas, where some of the biochemical services are primitive beyond belief, will continue to exist just as long as the clinicians are prepared to tolerate them.

One must have some sympathy for the plight of the poor young pathologist described by Professor Cappell, but if you stand at the crossroads for five or more years, trying to look north, south, east, and west simultaneously, what else do you expect but a pain in the neck? This wretched creature will probably finish up with a diploma in clinical pathology (which Professor Cappell curiously omitted to mention in his article), land in a tenth-rate laboratory, and spend most of his life doing routine blood-ureas—and serve him right for being such a fool! There is only one end to all this. Let the pathologist stick to his microscope and leave biochemistry to those who are qualified to practise the subject.

The Western Infirmary,
Glasgow

E. B. HENDRY
Consultant Biochemist.

ESSENTIAL HYPERTENSION

SIR,—You published on Oct. 8 and 15 two papers whose authors appear to make quite different assumptions about the nature of essential hypertension. Professor Brod tests a hypothesis about hæmodynamics in hypertension that is derived both in concept and in method from psychosomatic research. The concept of hypertension as a stress disorder was extensively discussed at a conference at the Royal College of Physicians in May, 1958, and I would recommend a study of the proceedings[1] to those who want to understand the background to Professor Brod's thinking about research.

The relevant observation is that hypertensive episodes spontaneously arising in people without cardiovascular disease, or that are experimentally provoked by an investigator, have a consistent emotional basis. This is an emotion best described as one of aggressive resentment arising in frustrating social and domestic situations and having an impulsive tendency to handle the situation by an inappropriate muscular aggression that has to be held in check.

These observations from the psychiatrist's couch lead to a prediction that an increased flow of blood in voluntary muscles should be a feature of hypertension that will become marked during pressor responses. Brod has shown just this. It also explains why he can make apparently sweeping conclusions, thus (p. 778) "the rise of blood-pressure . . . at any rate in the early stages, can accordingly be explained by the hypertensive being in a state of more or less permanent readiness for muscular action. This explanation differs from previous ones in that essential hypertension is not regarded as something newly acquired but simply as the result of disturbed regulation of one of the fundamental hæmodynamic responses of the organism "

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[1] *Lancet*, 1960, i, 1242.

[1] The Nature of Stress Disorder. Society of Psychosomatic Research. London, 1959.

To turn to the paper from the Social Medicine Research Unit, I know that the supporters of bimodal distribution *and* the supporters of continuous distribution of diastolic pressure in the population are all aware of some of the evidence about stress, but there is no evidence that they are integrating this into their thinking about this problem I think the stress concept allows that a continuous distribution in young adults may become a bimodal one in the middle-aged, when a psychophysiological response has become exaggerated into a disease of blood-vessels Professor Morris aims his research at the " common high blood-pressure without evident cause in middle age ", but I am sure from my own work and from that of Hines, whose writings are too well known to need quoting, that if we want to understand the nature of hypertension we must look at its uncomplicated beginnings in young adult life, where it seems to appear silently as a transient stress response from a quasi-normal baseline Begin here if you want to know the natural history of hypertension

For my part I do not think the primary disorder is high blood-pressure, but an excessive excitability of the diastolic pressure, that is one aspect of an excitability of the whole person This is why casual readings are so suspect There must be several genetic elements, but stress findings indict cultural elements which should be allowed for in evaluating resemblance in close relatives whom you may expect to have more family stress in common than they have inheritance

May I end on a thought-provoking question that was put from the chair at the conference on stress disorder in 1958 by Dr Fraser Roberts " Why should it be that so many of the diseases which are regarded as psychosomatic are the diseases which have a genetic component?" This question is a pointer towards a more rewarding multicausal approach Perhaps, like Professor Brod, investigators will have to start thinking about the whole person in his human setting

Cranbrook JOHN HAMBLING

SURGICAL REMOVAL OF BRANCHIAL SINUS

SIR,—I was interested to read Mr Small's account (Oct 22) of this operation I have not enough experience to comment on the debatable point of whether the lesion is primarily a fistula or a sinus, but I do recall one case where the dissection was facilitated by the preliminary injection of the track with gentian violet

In this instance the track seemed to end short of the pharyngeal wall, but I was intrigued to hear from the anæsthetist after the operation that the pharynx contained a lot of blue dye Fortunately a cuffed and inflated endotracheal tube had been employed and no harm resulted

Mr Small states that with the method he describes, intubation is preferable but not essential I feel, however, that regardless of technique—and despite the hazard recently reported by Dr Pryer and his colleagues (Oct 1)—where the incidence of a fistula as opposed to a sinus may be as high as a third of the cases, a cuffed and inflated tube should always be used

Stobhill General Hospital F T CROSSLING

NAMES OF DRUGS

SIR,—Would it not be possible for your journal to help further in the clarification of the vexed and complicated subject of the names of drugs?

In *The Lancet* of Oct 15, in a leading article on " Tranquillisers in Psychiatry ", you discuss, amongst other drugs, the use of methaminodiazepoxide The trade name is not mentioned In the correspondence columns are five letters concerning the side-effects of 'Librium' Neither the heading of the correspondence column nor any of the letters mentions the pharmacopœial name Only references to previous correspondence connect the two names. The trade names of some of the other drugs mentioned in the leading article may be less easy to find

The equivalence of pharmacopœial and trade names of drugs more recently introduced cannot yet have reached the standard works of reference, and it would be helpful if equivalent names were cited more frequently in current literature.

Bedford R G. MILLER

*** We are sorry we were not more helpful on the occasion Dr. Miller mentions In editorials we normally give approved or chemical names in preference to proprietary names, of which there may be several There is as yet no official approved name for methaminodiazepoxide ('Librium') and we used the non-proprietary name now in use Unfortunately we failed to include it in the group of letters published on Oct 15 —ED L

DIAGNOSIS OF FAT-EMBOLISM

SIR,—After reading Dr Sevitt's useful paper of Oct 15, I am prompted to draw attention to the valuable help in the diagnosis of fat-embolism afforded by ophthalmoscopy, *particularly in cases with " cerebral " symptoms.* The embolus can be seen as a highly refractile globule, lodging usually at the fourth or fifth branching of a retinal artery, the branches beyond being invisible This has repeatedly proved of invaluable help when peculiar neurological syndromes have presented in circumstances suggesting the possibility of fat-embolism The clinical picture may at times indicate dysfunctions in the midbrain or pons, and for that reason the term " cerebral " is inaccurate Obviously the disturbances produced must depend on the chance distribution of the major showers of emboli, and for that reason the pattern of neurological disturbance in these cases is far from stereotyped

When the emboli have lodged in the retinal arteries for a day or more their presence can be deduced by the finding of several small white patches with fluffy margins peripherally in the retina

Retinal emboli can be seen in cases with negative sputum and urine, and before petechiæ appear

Frenchay Hospital,
Bristol G L ALEXANDER

SIR,—I was extremely interested in Dr Sevitt's article He states that " aids to diagnosis would be most helpful in the severe cases without a rash " Although I can make no claim to experience, having seen, in my capacity as ophthalmologist, only one case, might I make a plea for routine examination of the fundus oculi in such cases?

A child of 9 was knocked down by a car and sustained a comminuted fracture of the proximal half of the left tibia and fibula She was unconscious when admitted to hospital and although she recovered after a short time, she remained drowsy and irritable Routine examination of the central nervous system revealed to an observant registrar a " hæmorrhage behind the pupil " and I was asked to give my opinion two days after the accident

There was no other injury, apart from the fractures The child had the irritable drowsiness that reminded me of tuberculous meningitis The pupils were slightly dilated, reacted sluggishly to light, and their reaction was ill sustained The ocular media were clear and the fundi showed an unusual picture Radiating from the upper and nasal aspects of each disc were striate hæmorrhages These coalesced near the disc but forked out towards the periphery for about two disc diameters In addition, many small striate hæmorrhages were scattered throughout each fundus although predominantly in the upper half Near the periphery and in the region of the maculæ the hæmorrhages were oval or round The configuration of these hæmorrhages probably depended on the density of the axons in the nerve-fibre layer of the retina. In addition, at the macula and at the periphery fluffy off-white " exudates " were seen Hair-like hæmorrhages were present in the papillo-macular bundle The fundi were observed for several days The hair-like hæmorrhages in the papillo-macular bundle faded in 48 hours but new ones recurred for about 6 days after the accident About this time the child's irritability and drowsiness disappeared and no new hæmorrhages were subsequently noted

The whole clinical picture could only be explained by postulating multiple minute fat-embolic, although at no time was a rash observed and two examinations of the urine revealed no fat globules

Bury General Hospital,
Lancs
J McLENACHAN

DIAGNOSIS OF DIABETES

SIR,—In your leading article of Oct 1 you refer to the indings of Reid[1] that 48% of 352 diabetics seen in Dundee had symptoms for more than four months when he disease was diagnosed and 20% had symptoms for more than a year If these high percentages are general hroughout the country there would indeed be complete ustification for your view that " such a state of affairs should no longer be tolerated " However, I wonder if the picture is really quite so dark as would appear from the igures you quote? My own corresponding figures in a study of 300 patients seen at the Royal Devon and Exeter Hospital[2] show that 27% had symptoms for more than four months at the time of diagnosis and 15% had symptoms for one year or more

Further analysis of this series reveals that in 12 (4%) cases the onset was acute and the diagnosis was made within six days of the presenting symptoms In 5 of these patients the exact day or even hour of onset was known. In 13% of diabetic patients symptoms preceded diagnosis by a period of from seven days to one month, and 18% had symptoms for more than one month and less than two months, while 14% had symptoms for more than two months and less than three months

I would suggest, however, that all surveys based on personal interview or questionary are open to criticism as is evident from the fact that in approximately two-thirds of my cases the onset of symptoms was so insidious that the patient was unable to define this accurately, even to within a two-month period. An indefinite onset of this nature was recorded in 75% of patients over 40 years of age and in 78% of patients without ketonuria It is in this particular group of older diabetic patients without ketosis that there is so often a long delay in diagnosis

Your leader also states that " at present diabetes mellitus is usually diagnosed when the patient reports with symptoms due to the primary disorder or, in about 20% of cases, to complications of the disease "[3] In 95% of the Exeter patients the presenting symptom was one of the accepted classical symptoms of diabetes—namely, polyuria, polydypsia, polyphagia, loss of strength, or loss of weight. All five symptoms were present in 19% of patients, occurring in 24% of cases with ketosis and 15% of cases without ketosis, and were reported over twice as often in patients under 40 as in those over 40 However, in 44% of diabetic patients the presenting symptoms were multiple and 46% of these symptoms were due to complications of the disease There is certainly, as you say, a widespread tendency to misinterpret the symptoms of this disease Those which you select as being particularly liable to misinterpretation accounted for a high proportion of presenting symptoms in this survey—thirst (48%), polyuria (15%), loss of weight (14%), visual impairment (6%), and pruritus vulvæ (in 27% of females over 16 years of age), and genital puritus in men (4%)

With regard to your statement that " some of the delay in diagnosis is doubtless due to imperfections in the practice of doctors who fail to test the urine when the clinical picture suggests diabetes ", I feel that it is only fair to mention that in 240 (80%) of 300 patients in this Exeter survey the diagnosis was made by the family doctor 25 new cases presented as severe diabetic ketosis or coma and in only 5, simulating acute abdominal emergencies, was the condition not recognised before admission to hospital In 12 (4%) cases symptomless glycosuria of diabetic origin was an incidental finding at a routine medical examination or when the patient was seen for an unrelated condition The remaining 48 (16%) were first diagnosed in hospital. These patients attended with diabetic symptoms or complications although their nature had not been previously recognised

As you say, there is no doubt that much of the delay in diagnosis is due to ignorance among the lay public. This view is confirmed by my findings that in only 2 of 300 diabetic patients was the diagnosis made before a doctor was consulted, and this was only so because in each case the patient's wife was a trained nurse and recognised the symptoms of the disease. As my survey was completed some five years ago it is possible that the lay public is now better informed through, for example, the medium of television

May I emphasise that I do not wish to detract in any way from the views in your leading article concerning the fundamental importance of early diagnosis of diabetes, but I felt that, in fairness, one should point out that the figures quoted in support of your thesis may well not be representative of the country as a whole A lowered incidence of the classical symptoms of this disease can be expected only if early diagnosis is achieved One way of attaining this object would be to act upon the suggestion made by Dr Joslin[4] almost forty years ago that every person should have the urine examined for glucose on his or her birthday

Princess Margaret Hospital,
Swindon
A G FREEMAN

Appointments

CHARLES, A. H, T.D, M.A., M.B Cantab, F.R.C.S., F.R.C.O G consultant gynæcologist, Royal National Orthopædic Hospital, London.

BEASLEY, ROSEMARY A., M.R.C.S., D OBST assistant M O.H. and school M.O, Coventry

CARUANA, SALVINO, M.D Lpool, D T.M. & H, D.P H. assistant M.O, Cheshire.

DOWNSBROUGH, F K., M.B Leeds, D.M.R.D consultant radiologist (neuroradiology), Derby group of hospitals

FRYER, ADA M., M.B Glasg, D OBST assistant M.O.H. and school M.O, Coventry

GILBERT, BASIL, M.R C.S, D.P.H deputy M O H. and deputy principal school M.O, Sunderland.

East Anglian Regional Hospital Board

BANERJEE, M S, M.B. Calcutta, D G O registrar in obstetrics and gynæcology, Norfolk and Norwich hospital group

BLUMBERG, N A M.B W'srand, F.R.C.S surgical registrar, Ipswich and East Suffolk hospitals

DAY, GEORGE, M.A., M.D Cantab consultant physician-superintendent, Mundesley Hospital

GOSS, G C. L., M.B. Lond registrar in psychiatry, Hellesdon Hospital

LLOYD, A. T, M.B Brist D.P.M senior registrar in psychiatry, Fulbourn and Addenbrooke's hospitals

McKECHNIE IAN, F.R.C.S.E consultant orthopædic surgeon, Peterborough and Stamford hospital group

MEHTA J S, M.B Bombay radiological registrar, Ipswich and East Suffolk Hospital

PEARS M A, M D Lond, M.R.C.P consultant physician, King's Lynn hospital group

VARSAMIS I, M.B Alexandria registrar in psychiatry, St. Andrew's Hospital Norwich.

WALLACE, SHEILA M.B Lond, D OBST pædiatric registrar, Ipswich and East Suffolk Hospital

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[1] Reid, J J A *Med Offr*, 1960 103 325
[2] Freeman A G *Brit med J* 1955, i 1149
[3] Beaser, S B *New Engl J Med* 1948, 229, 765
[4] Joslin, E. P *J Amer med Ass* 1921, 76, 79

Notes and News

INTERNATIONAL FEDERATION OF SURGICAL COLLEGES

THIS Federation was inaugurated in Stockholm in July, 1958, and some of its objects are to improve and sustain standards of surgery throughout the world, to maintain close relations among approved surgical colleges and institutions, and to maintain high standards of education, training, and research At a meeting in Munich in September, 1959, working parties were established to examine the following subjects surgical missions, training of surgeons, surgical research, and the interchange of young surgeons A gathering of the Federation at the Royal College of Surgeons in London on Oct 18–20 was attended by representatives of the 24 member institutions It began with meetings of the working parties, and the later proceedings included two sessions on new research work, one contributed by the American College of Surgeons, and the other by the surgical colleges in the British Isles Prof Digby Chamberlain and Mr Harold Edwards described the teaching of surgery as it was undertaken at the Royal College of Surgeons of England, and visitors were also able to see something of the postgraduate course organised by the Institute of Basic Medical Sciences and to inspect the scientific departments and museums of the college

At a dinner on Oct 19 in the Edward Lumley Hall of the college, the Minister of Health, Mr Enoch Powell, proposed The Federation, and its president, Sir Harry Platt, responded The president of the college, Sir Arthur Porritt, then formally admitted to honorary fellowship Prof E Dahl-Iversen, of Copenhagen, who was introduced by Prof Ian Aird, and Prof J F Nuboer, of Utrecht, who was introduced by Prof Digby Chamberlain

During the meeting the Duke of Edinburgh visited the college and took tea with the council of the Federation

KYASANUR FOREST DISEASE

AT a meeting of the Royal Society of Tropical Medicine and Hygiene in London on Oct 20, Dr Telford H Work presented a film entitled *Kyasanur Forest Disease in India* and gave a detailed commentary The disease first appeared in southern India after many deaths had been noticed in December, 1955, among monkeys in the Kyasanur forest The dead monkeys exhibited bleeding from the nose and anus, and when permission to shoot monkeys from the forest was obtained it was found that they invariably harboured ticks Human cases of the disease were characterised by very sudden onset, high fever, headache, and great prostration The fever, which usually lasted between five and twelve days, was associated with pronounced stiffness of the muscles of the neck and lumbar regions and, on or about the third day of the illness, with bleeding from the gums and tarry stools Death when it occurred was usually between the seventh and tenth days of the fever, and necropsy revealed focal necrosis in the liver but no encephalitis Among early cases the mortality was 28% but later this was reduced to 4–6% The virus was isolated It belongs to group B of the Arbor viruses and is transmissible by the ixodid ticks found on the monkeys, and a vaccine has now been prepared from it

CANCER IMMUNISATION IN SWEDEN

IN the past two years clinical tests of a cancer vaccine and a cancer serum have been carried out at Radiumhemmet in Stockholm on inoperable cases Preliminary reports by Dr Bertil Björklund, who is in charge of the Immunological Research Laboratory in Stockholm, and by Dr Lennart Malmquist, who is attached to Radiumhemmet, have appeared in *Svenska Läkartidningen* for Oct 7 The vaccine is an antigen obtained from mass cultures in vitro of a cancer strain grown continuously for ten years The serum was derived from horses immunised by antigens from necropsy material, and, more recently, also by purified antigen from in-vitro cell cultures Only the active globulin fraction of the serum is given to the patient Various dosages and modes of administration have been tried The vaccine is given intracutaneously, and the serum intravenously and also by injection into the tumour In two patients the serum provoked such violent pain in the tumour itself that the injection had to be discontinued and a narcotic administered intravenously Five cases are reported in detail Striking improvement was observed in several patients Case 5 was typical a patient born in 1899 was found in November, 1959, to have cancer of the gums and mouth Radiotherapy proved ineffective, and in March, 1960, the case was considered inoperable Serum and vaccine treatment was started in April, 1960 By the middle of May the tumour had notably regressed, and by June 3, 1960, it was held to be operable and was removed The patient died ten days later of " circulatory insufficiency " At necropsy no metastases were found

The National Cancer Institute of the U S Public Health Service has made a grant to Radiumhemmet to promote this research

THE RETREAT

TOWARDS its fund for reconstruction, this independent mental hospital has received nearly £150,000, and its new nurses' training school was opened by the Earl of Feversham on Sept 19 Other additions made during the past year include a new men's admission ward To bring the whole hospital correspondingly up to date will need a good deal more money, and donations, covenants, or legacies will be gratefully received by the treasurer, The Retreat, 107, Heslington Road, York.

In the 163rd annual report of the physician superintendent, Dr C C Beresford says that in 1959 the average number of patients in residence was 236 As in other mental hospitals, this figure is about 10% lower than in the peak years of 1956–57, but admissions, at 404, remain high Because more is done in outpatient departments and day hospitals the work of The Retreat becomes steadily more arduous " The type of case that comes into hospital now is rarely the average straightforward disease but the atypical, complicated or severe example of it " Dr Beresford welcomes the present movement as a healthy one " for far too long have many patients who could have been treated at home been obliged to enter a mental hospital or not receive any treatment at all " Nevertheless, he is inclined to think that the tendency to treat people as outpatients whenever this is possible is going too far, and, if it goes further, a reaction will follow, with a bigger proportion of cases treated in hospital " Certain illnesses in fact do far better in hospital For example, one can cite the addiction neuroses, the senile psychoses, and those who have become ill because of intolerable environmental strain"

The scope of day treatment at the hospital has been enlarged, and the number of consultation centres has been extended But Dr Beresford believes that time will show that the need for an essentially residential treatment unit such as The Retreat is as great as ever Thanks to the Mental Health Act, patients can now be admitted as to any other kind of hospital " This may sound to many a trivial matter " but " in fact it is of the greatest importance " The mental hospital is now allowed to admit any patient who does not refuse such treatment, without any of the previous formalities It is hoped that eventually, under the new Act, the patient contending with his illness will no longer have to contend also with the legal and popular prejudices that went with it

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University of Oxford

On Oct 13 the following degrees were conferred in absentia

D.M—P D Wall
B.M—Anne Stern

University of Birmingham

The title of professor of physiological chemistry has been conferred on Dr W Y Thorpe, formerly reader in chemical physiology

University of Edinburgh

On Oct 22 the degrees of M B, CH B were conferred on Louise F Fairley

University of London

Mr W T Irvine, reader in surgery at London Hospital Medical College, has been appointed to the chair of surgery at St. Mary's Hospital Medical School

Mr Irvine, who is 35 years of age, graduated B SC from the University of Glasgow in 1944 and M B in 1947 He held house-appointments before serving as a surgical specialist with the R.A M C from 1950 to 1952 After spending a year as surgical registrar at the Western Infirmary, Glasgow, he became Archibald fellow in experimental surgery at McGill University In 1955 he was awarded a Mayo Foundation fellowship in physiology at Rochester, Minnesota In 1956 he returned to Glasgow and was appointed lecturer in surgery at the Western Infirmary He took the degrees of CH M and M.D of Glasgow both with honours He has held the readership in surgery at the London Hospital since 1957 His published work includes papers on lymphosarcomata of the small intestine, late complications of uretero-colostomy, and the diathermy treatment of bladder papillomata He has also published many papers on the mechanism of gastric secretion and on various aspects of gastroenterology Recently he has been responsible for introducing isolated perfusion techniques with cytotoxic agents using the heart-lung machine for advanced malignant conditions

Dr D R Laurence, senior lecturer at University College and University College Hospital Medical School, has been appointed to the readership in pharmacology and therapeutics at the College and School The title of reader in tropical hygiene has been conferred on Dr B B Waddy in respect of his post at the London School of Hygiene and Tropical Medicine

University of Sheffield

Mr S D Clarke has been appointed lecturer in surgery, Mr D G Taylor part-time lecturer in cardiothoracic surgery, Mr A B Nutt part-time lecturer in ophthalmic surgery, and Dr R S Morton part-time lecturer in venereal diseases

Royal College of Physicians of London

On Oct 18 the Weber-Parkes prize was presented to Sir Geoffrey Marshall, and the Moxon medal to Professor John McMichael, F R S

The Registrar said that Sir *Geoffrey Marshall* early developed an interest in chest disease and particularly tuberculosis, and with his appointment to Guy's Hospital this interest quickened and he attained a considerable reputation as a teacher Early in the chemotherapeutic era he became chairman of the chemotherapy of tuberculosis trials committee of the Medical Research Council—work of the highest importance He also took a leading part in the formation of the Association for the Study of Diseases of the Chest, later known as the Thoracic Society, and he became its president He was later president of the Royal Society of Medicine In his counselling and advice his example over the years had been and continued to be a great stimulus to his colleagues both young and old

Presenting the Moxon medal, the Registrar emphasised Professor McMichael's prowess as a clinician, as a pioneer of modern scientific medicine, particularly concerned with investigations, and as an administrator In the clinical field he had become a consultant's consultant His pioneer work in cardiac catheterisation and percutaneous hepatic biopsy had been opposed and even condemned by more conservatively minded physicians McMichael, however, had the vision to see that accuracy of diagnosis was in the best interests of his patients, and today these methods were used throughout the world As an administrator, McMichael had played a very important part in the evolution and development of full-time university units in departments of medicine throughout Great Britain and in the Commonwealth His experience and progressive views in this rapidly developing aspect of medical education were second to none He was now an international figure of modern world medicine

Royal Australasian College of Physicians

On Oct 10 the following were admitted to the membership

J S Duke M T Havyatt, I J Mackie, F L. Rothwell, G S Walker (New South Wales), J K. Dawborn, J E Gault, B C. Ritchie (Victoria), A. G Collins, R. L. Hodge D A Kennedy, T A White (South Australia), J E Edwards, John Ferguson, E D O'Callaghan (Queensland), D H Gutteridge (Western Australia)

Royal Medico-Psychological Association

On Friday, Nov 18, at 2 15 P M , at 1, Wimpole Street, London, W 1, Dr Eliot Slater will give a Maudsley lecture His subject will be Hysteria 311

Royal College of Surgeons of Edinburgh

At the annual meeting of the college, held on Oct 19, the following office-bearers were elected

President, Prof John Bruce, vice-presidents, Prof Norman Dott and Mr W W Galbraith, secretary, Mr J A. Ross, treasurer, Mr J J Mason Brown, President's council, Mr David Band, Dr J B Dewar, Mr I L. Dick, Prof D M. Douglas, Mr C W A Falconer, Mr A. J C Hamilton, Mr J N Hartley, Prof R. J Kellar, Dr R. G Macbeth, Dr D S Middleton, Prof G I Scott, Mr R. L Stewart, Mr T I Wilson, representative on the General Medical Council, Mr K Paterson Brown, conservator of museum, Prof E C Mekie, hon librarian, Sir Walter Mercer

The following were admitted to the fellowship

R. Hanif Ahmed, Raja Ghulam Asghar, Syed Abbas Askari, M P Awon, Manickavasagar Balasegaram, Fiona M Bennett, R. K. Berry, D E Burgess, C. W Packiaratnam Canagaretna, D B Chapman, S D Clarke, J L Clarke, J L. Colvin, J Y Crooks, R. B Davey, Venkatrao Dawle, J A. S Dickson, T Satya Doss, E I P Ebosie, E A Elebute, Sudhir Kumar Ghose, Sah Dev Gupta, Umesh Chandra Gupta, Khin Maung Gyi, K. I M Heath, Guruprasad Sidhraj Hiremath, R. S Hole, Daniel Hugo, J A Hyde, J O'H Hyde, H B S Kemp, I R Kernohan, Indru Tekchand Khubchandani, Ram Partap Kumar, J B Laine, R. A Leggatt, Greta I Leitch, Franklin Wang-Pong Li, Gordon Low, Earl Ming-Teh Lu, D J McAuliffe, Jean M M McKenzie, J H McKessar, Madavilakom Padmanabhapillay Manomohan, Mohamed Abdel Kader Mohamed Mansour, M D Middleton, L. J Phillips, P A M. Pozzi, Nagesh Mukund Prabhu, K. Alagamuthu Ramalingam, Mohini Vasanmal Ramchandani, Vinodray Dhirajlal Raval, D M. Ritchie, Adnam Sarsam, I G Schraibman, Alan Simpson, J W Smith, M G H Smith, Dhun Dinshaw Sumariwalla, G R. Thoms, R. S Todd, P J Venter, J P A Weaver, D G Wray, I W M. Wright, Jayaraja Yogaratnam

Faculty of Radiologists

On Nov 19 and 20 at the Royal College of Surgeons, Lincoln's Inn Fields, London, W C 2, this Faculty will hold a postgraduate weekend course Further particulars may be had from the secretary of the Faculty, 47, Lincoln's Inn Fields, W C.2

On Friday, Nov 18, at 4 30 P M., at the Royal College of Surgeons, Prof R. W Scarff will give a Skinner lecture on prognosis in carcinoma of the breast

Royal National Throat, Nose, and Ear Hospital, London

The trustees of the Nuffield Foundation have increased from £60,000 to £100,000 their grant for the erection of the Nuffield hearing and speech centre attached to this hospital Building work is expected to begin early next year

National Society of Children's Nurseries

On Thursday, Nov 10, at 10 15 A M., at County Hall, London, S E 1, this society will hold a conference on Working Wives—What of the Children? The speakers will include Dr W Lumsden Walker, Dr Bryan Reffold, and Dr Dayid Morris

Genetics, Statistics, and Radioisotopes

The Institute of Basic Medical Sciences will hold a course on this subject on Monday, Oct 31, and Nov 1 and 2 Further particulars may be had from the secretary of the Institute, Royal College of Surgeons, Lincoln's Inn Fields, London, W C 2

College of General Practitioners

Public Welfare Foundation Prize—This competition (six prizes of £40) is designed to encourage senior medical students in the United Kingdom and Eire who have taken advantage of opportunities to discuss the diagnosis and management of patients in the setting of general practice Details may be had from the dean of the students' medical school or from the secretary of the college, 41, Cadogan Gardens, London, S W.3

Rockefeller Foundation

During the third quarter of 1960 the Foundation made grants of over $2 million Those for medical and natural sciences amounted to over $1 million These include a five-year grant of $43,500 for research in human genetics under Prof L. S Penrose at University College, University of London, and a three-year grant of $30,000 for the continuation of work on the ultrastructure of nucleic acids, the fine structure of muscle, and the chemical behaviour of chromosomes under Prof J T Randall at King's College, University of London

Mr J F Hunt has been appointed controller of supplies at the Ministry of Health in succession to Mr A D Campbell who is retiring

On Wednesday, Nov 2, at 5 15 P M, at the Royal Free Hospital, Gray's Inn Road, London, W C 1, Dr F J W Miller will speak on the Thousand Families Survey

At a meeting of the Medical Electronics Discussion Group on Friday, Nov 4, at 6 P M, at the Institution of Electrical Engineers, Savoy Place, London, W C 2, there will be a discussion on electroconvulsive therapy The opening speakers will be Dr A Spencer Paterson and Mr W H Stanton

A meeting for general practitioners will be held on Sunday, Nov 6, at 10 15 A M, at University College Hospital, London, W C 1 Prof A S Prophet will speak on dental emergencies in general practice

On Wednesday, Nov 9, at 8 15 P M, at the General Infirmary at Leeds, the Yorkshire Society of Anæsthetists will hold a symposium on the North American Anæsthetic Scene The speakers will be Dr R P Harbord, Dr Gwendolen Harrison, and Dr F G Mackintosh

The Royal College of Nursing has received from the Privy Council the orders in council allowing the necessary alterations to its royal charter and by laws to extend its membership to male nurses From Nov 1 men and women holding the qualification of State-registered nurse, registered mental nurse, registered nurse for mental defectives, registered nurse for sick children, and registered fever nurse will be eligible for membership

The 1960–61 programme of Galenicals, the student society School of Medicine of the University of Bristol, will inclu following addresses Sir Robert Macintosh, An Anæsthetist U S S R and China, Nov 4, Dr R E Hemphill, *Psycho* Disorder and the Artist (presidential address), Nov 18, Dr Asher, The Sins of Medical Students, Dec 2, Dr Ma Critchley, The Medical Aspects of Oscar Wilde, Jan 20, Prof Browne, My Experience in a University Department of Indu Health, Feb 17, Mr Norman Lake, The Effects of Low Tempe and Resuscitation on Living Tissues, March 3, Sir Henry D Royal Society of London and Medical Science—a record years, March 17 The secretary of the society is Mr A. Dickens, Students' Common Room, Bristol Royal In Bristol, 2

The annual dinner of the Glasgow University Club, Lond be held at the Trocadero Restaurant, London, W 1, at 7 on Thursday, Nov 10 Particulars may be had from Dr. Heggie, department of pathology, North Middlesex Hospital,

A semi-permanent exhibition will be held at the Insti Dermatology, Lisle Street, London, W C 2, from Nov 7 by Dr P D *Samman on cutaneous tuberculosis and sarcoid*

The National Corporation for the Care of Old People has co a register of research that is being done on social and socio aspects of the welfare of the elderly Only work that has progress since 1955 has been included Copies of the regist post free) may be had from the Corporation, Nuffield Lodge, R Park, London, N W 1

Diary of the Week

OCT 30 TO NOV 5

Sunday, 30th

Institute of Laryngology and Otology, 330, Gray's Inn Road, W C 1
10 15 A M Mr S E Birdsall Common Ear, Nose, and Throat Conditions

Monday, 31st

Postgraduate Medical School, Ducane Road, W 12
4 P M Dr Wilfred Sircus Practical Application of Gastric Secretion Studies
Institute of Obstetrics and Gynæcology
4 30 P M (Queen Charlotte's Maternity Hospital, Goldhawk Road, W 6) Mr G W *Garland Antenatal Supervision*

Tuesday, 1st

Royal College of Surgeons of England, Lincoln's Inn Fields, W C 2
5 P M Mr N H Porter Physiological Study of the Pelvic Floor Muscles in Rectal Prolapse (Arris and Gale lecture)
University of London
5 15 P M (Middlesex Hospital Medical School, Mortimer Street, W 1) Prof Hans Schaefer (Heidelberg) Principles of Circulatory Regulation (First of two lectures)
British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Prof Michael Stoker Latent Virus Infections
St Mary's Hospital Medical School, W 2
5 P M (Wright Fleming Institute) Mr Elliot Philipp Antepartum Hæmorrhage
West End Hospital for Neurology and Neurosurgery, 91, Dean Street, W 1
5 30 P M Dr H C Grant Chronic Meningitis
Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr A D Porter Keratinisation, Normal and Abnormal
Leeds Neurological Sciences Colloquium
5 15 P M (General Infirmary at Leeds) Dr W Ritchie Russell Neurological Aspects of Memory

Wednesday, 2nd

Royal College of Surgeons of England
5 P M Dr J B Enticknap Coronary Thrombosis and Other Forms of Ischæmic Heart Disease (Erasmus Wilson demonstration)
University of London
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr Charles Wilcocks Aspects of Medical Investigation in Africa Tuberculosis (First Heath Clark lecture)
Royal Society of Medicine, 1, Wimpole Street, W 1
5 15 P M *History of Medicine* Sir Philip Manson-Bahr Malaria Story
Postgraduate Medical School
2 P M Prof R H S Thompson Biochemistry of Multiple Sclerosis
Royal Institute of Public Health and Hygiene, 28, Portland Place, W 1
3 30 P M Mr F Ward Flammability of Textiles
Institute of Dermatology
5 30 P M Dr Arthur Tickner Biochemistry of Pigmentation
Institute of Diseases of the Chest, Brompton, S W 3
5 P M Dr W D W Brooks Spontaneous Pneumothorax
London Amateur Boxing Association
8 P M (British Railways Film Unit, Savile Row, W 1) Dr J L Blonstein Olympic Games in Retrospect
Assurance Medical Society
5 P M (11, Chandos Street, W 1) Mr R E Beard Thoughts on Mortality, Morbidity, and Medical Underwriting
Midland Medical Society
8.30 P M (Joint meeting with Midland Counties Veterinary Association, Birmingham Medical Institute, 36, Harborne Road, Edgbaston) Dr J Deans Rankin, Dr K B Rogers Diseases of Animals Communicable to Man
Manchester Medical Society
4 30 P M (Medical School, University of Manchester) M Dr C J Hodson Radiological Observations on the History of Chronic Pyelonephritis
University of Leeds
5 P M (*General Infirmary at Leeds*) *Mr D W Currie Cancer* Female Genital Tract
6 P M Mr Herbert Agar General Surgical Problems in Gynæcolo
Medico Chirurgical Society of Edinburgh
8 30 P M (Royal College of Surgeons of Edinburgh, 18, Nicolson Prof R B Hunter Therapeutics 1960

Thursday, 3rd

Royal College of Physicians, Pall Mall East, S W 1
5 P M Dr W I Card Concept of Gastric Secretory Cell Mass shaw lecture)
University of London
5 P M (*1, Wimpole Street, W 1*) *Dr Paul H Holinger* (Ch Clinical Aspects of Congenital Anomalies of the Larynx, T Bronchi, and Œsophagus (Semon lecture)
5 15 P M (Middlesex Hospital Medical School) Professor S Theory and Interpretation of the Electrocardiogram (Se *two lectures*)
5 30 P M (London School of Hygiene and Tropical Medicin Wilcocks Aspects of Medical Investigation in Africa—somiasis (Second Heath Clark lecture)
British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine) Dr Rundall Regular Folds in Protein and Polysaccharide Cha
Institute of Psychiatry, Maudsley Hospital, Denmark Hill, S E 5
5 30 P M Dr Catherine Hebb Intracellular Structures and Tran Substances in the Nervous System
Nuffield Orthopædic Centre, Oxford
8 30 P M Mr H V Crock Experiments on Spinal Fusion in th
North Western Thoracic Society
5 P M (Aintree Hospital, Liverpool) Dr John Howell, Dr Ogilvie Physiological and Clinical Aspects of "CO, Rete
Honyman Gillespie Lecture
5 P M (University New Buildings, Teviot Place, Edinburgh) Prof Kellgren Osteoarthrosis in Patients and Populations

Friday, 4th

Royal Society of Medicine
10 30 A M *Otology* Mr J P Monkhouse Triumphs and Proble *Middle-ear Surgery* (*Presidential address*)
2 30 P M *Laryngology* Mr J H Otty Retrospect and Pr (Presidential address)
4 P M *Anæsthetics* (Royal College of Surgeons) Dr R M (Boston) Anæsthesia for Emergency Procedures in Childre
Postgraduate Medical School
10 A M Mr K C McKeown Gastrectomy in Peptic Ulcer
4 P M Dr B E C Nordin Osteomalacia and Osteoporosis
Ciba Foundation
5 P M (66, Portland Place, W 1) Prof J Konorski (Warsaw) C Concepts Concerning Physiological Mechanisms of Animal Behaviour
Institute of Laryngology and Otology
3 30 P M Dr Imrich Friedmann Advances in Chemotherapy
Institute of Obstetrics and Gynæcology
3 P M (Chelsea Hospital for Women, Dovehouse Street, S W 3) E C Amoroso Endocrinology of Pregnancy
Association of Anæsthetists of Great Britain and Ireland
9 15 A M (Royal College of Surgeons) Opening of two day mee
Plymouth Medical Society
8 30 P M (North Friary House) Mr G L Alexander Danger S Cases of Head Injury

Saturday, 5th

Institute of Laryngology and Otology
Noon Dr Holinger Endoscopy in Otolaryngic *Pathology*